The weight of *subclinical vascular disease & neuroticism in* late-life depression

Radboud M. Marijnissen

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CHAPTER 1

General introduction

Depression in later life

Major depressive disorders commonly occur in older adults, with a pooled prevalence rate of 1.8% for community-living people aged 55 years and older and a pooled prevalence rate of 9.3% for older persons aged 75 years when institutionalized persons are also taken into account (Beekman et al, 1999; Luppa et al, 2012). The spectrum of depressive symptoms however ranges from mild 'subthreshold' conditions to major depression meeting the criteria for a psychiatric disorder (Riedel-Heller et al 2006; Fiske et al, 2009). Minor depression has been found to be more prevalent in community-dwelling older adults with a prevalence of 9.8% (Beekman et al, 1999) and based on cut-off score on a depression severity measure, clinically relevant depressive symptoms are even more prevalent (respectively 13.5% and 17.1%) (Beekman et al, 1999; Luppa et al, 2012). Depressive symptoms in late life are highly persistent (Luppa et al, 2012). Late-life depression has a chronic course in both the younger elderly (Beekman et al, 2002) as well as the oldest-old (Stek et al, 2006). Moreover, older people have a greater risk of recurrence of depression than younger adults (Licht-Strunk et al, 2007; Mueller et al, 2004).

Depression in later life has been consistently associated with negative consequences irrespective of whether depression is defined as depressive symptoms, minor or subthreshold depression or major depressive disorder. One may thus ask whether the diagnostic cut-off applied in the classification system DSM-IV (Diagnostic and Statistical Manual for Mental disorders) is specifically-tailored enough for late-life depression. These negative consequences include a higher incidence of several age-related diseases like cardiovascular disease, stroke, diabetes and obesity morbidity (Penninx et al, 2013), functional decline and even a higher mortality rate. Not surprisingly, late-life depression is associated with a poorer self-rated health and decreased quality of life. From a societal perspective, increased days lost due to disability (Beekman et al, 1995; Fiske et al, 2009) and increased health care utilization and direct costs (Katon et al, 2003; Luppa et al, 2008), probably due to experiencing functional disability and cognitive decline (Dombrovski et al, 2007; Lenze et al, 2005) can not be neglected.
A complicating factor in clinical care, however, is the diversity in symptoms, presumed pathophysiological mechanisms and consequences for that individual depressed patient we see in our practice. Accumulating evidence show that depressive disorder is a heterogeneous condition with respect to its phenomenology as well as its underlying pathophysiological mechanisms (Shafer, 2006; de Jonge et al, 2006; Wardenaar et al, 2010; Ormel & de Jonge, 2011). This heterogeneity is assumed to increase with advancing

age and when taking subthreshold forms of depression into account. This thesis is devoted to further unravel heterogeneity with respect to symptom profiles of depressive symptoms in relation to two major pathways leading to late-life depression, i.e. vascular disease burden and neuroticism.

Phenomenological heterogeneity: Depressive symptom profiles

The DSM-classification system has specified several subtypes of depressive disorder, based on severity, course or actual symptoms. Based on the severity of actual symptoms, depressive disorder may be specified as mild, moderate or severe and based on the symptom profile further specified as with anxious distress, mixed features, melancholic features, atypical features, catatonia or psychotic features. Nonetheless, these severity specifiers may only be applied when a patient meets the general criteria of a depressive episode. This is made possible by applying a polythetic definition (that is a patients needs to satisfy some but not all symptoms) as well as by defining individual criteria in two directions (for example psychomotor retardation versus agitation, weight loss versus weight gain).

Irrespective of this diversity, several observer-rated and self-rated instruments have been developed to measure the severity of depression. As can be expected, factor analyses of these questionnaires often show two or more dimensions (e.g. Beck & Steer, 1987; de Jonge et al, 2006). For example, the most often-used depression severity instrument, the Hamilton Depression Rating Scale, appears to be multidimensional. A large study on depressed outpatients identified four subscales, referring to 1) somatic anxiety, 2) psychic anxiety, 3) core depressive symptoms and 4) anorexia (Pancheri et al, 2002), although several other solutions have also been reported (e.g. Bech et al, 1981). In this thesis, symptom profiles will be based on the Inventory of Depressive Symptoms self-report (IDS-SR) and on the Beck Depression Inventory (BDI). The IDS-SR is an increasingly-used instrument that covers both the key symptoms of depression and somatic/vegetative symptoms, originally developed to measure severity of overall depression (www.idsqids.org) (Rush et al, 1996). In a sample of depressed older persons, three dimensions have been identified, including a mood, a motivation and a somatic dimension (Hegeman et al, 2012). The BDI is one of the most frequently used self report instruments to assess depressive symptoms and its factor structure has often been examined, mostly resulting in two (Beck and Steer, 1987) or three dimensions (Morley et al, 2002; de Jonge et al, 2006).

Pathways to late-life depression

Two prospective predictors of late-life depression are neuroticism (Steunenberg et al, 2006) and vascular disease (Taylor et al, 2013; Valkanova & Ebmeier, 2013). In the past decade, most research has focused on the role of vascular disease (Sneed et al, 2008; Ormel & de Jonge, 2011; Taylor et al, 2013), whereas neuroticism has less frequently been investigated in old age psychiatry. Both (major) pathways may act to a certain degree in individual patients. In this thesis, the vascular pathway will be examined with respect to subclinical vascular disease and also in interaction with neuroticism.

Vascular depression and subclinical vascular disease

In 1997 Alexopoulos and colleagues (Alexopoulos et al, 1997) and Krishnan and colleagues (Krishnan et al, 1997) independently postulated the 'vascular depression hypothesis' stating cerebrovascular disease may predispose, precipitate or perpetuate some geriatric depressive syndromes. The group of Alexoupoulos substantiated this hypothesis primarily with epidemiological findings on the (reciprocal) relationship between vascular disease and depression and a late-onset depressive subtype. Krishnan and colleagues substantiated this hypothesis on an increased severity of white matter hyperintensities (WMH) in depressed compared to non-depressed older persons seen on T2-weighted or fluid-attenuated inversion recovery MRI (Coffey et al, 1989). In patients with late-life depression, these WMH are presumed to be of ischemic origin due to its association with cerebrovascular risk factors, including diabetes, cardiac disease and hypertension (Thomas et al, 2002; Taylor et al, 2005; Mast et al, 2008; Goodman et al, 2008; Taylor et al, 2013). In general, the phenomenological expression of vascular depression is characterised by apathy, psychomotor retardation, cognitive deficits, lack of insight and disability disproportional to the depression severity (Taylor et al, 2013), whereas a low mood and feelings of guilt or worthlessness are less pronounced. This might be explained by ischeamic damage to specific white matter fiber tracts, including the cingulum bundle, uncinate fasciculus and superior longitudinal fasciculus (Sheline et al, 2008; Dalby et al, 2010; Taylor et al, 2011) leading to executive function deficits in neuropsychological testing (Smith et al, 2011) and apathy and loss of interest as clinical features (Esposito et al, 2010). In its most advanced form, vascular depression would approximate post-stroke depression (Aben et al, 2002). Further refinement of the vascular depression hypothesis has culminated in a depressive-executive dysfunction syndrome (Alexopoulos et al, 2001). Until now, the evidence for a real distinctive disorder remains limited with many inconsistent results (Baldwin et al, 2005).

Thus far, epidemiological studies on vascular depression classify people as vascular compromised in case of cerebro- and/or cardiovascular events. These studies thereby ignore the fact that many older people do have significant subclinical vascular damage reflected in increased levels of vascular risk factors (e.g. metabolic syndrome) and significant atherosclerosis throughout the body. Atherosclerosis is a gradual process, which already starts in early adolescence and may remain asymptomatic for decades before the manifestation of clinical events at later age (Ross, 1993). To date, the association between subclinical vascular disease and depression has hardly been examined. In this thesis, we focus on the association between different depressive symptom dimensions on the one hand and atherosclerosis, metabolic syndrome and obesity on the other hand. Since patients with obesity, metabolic syndrome and/or advanced levels of atherosclerosis do not necessarily have experienced a vascular event, we use the term subclinical vascular disease collectively for obesity, metabolic syndrome and/or atherosclerosis in the introduction and summary of this thesis.

Atherosclerosis will be based on the carotid intima-media thickness (cIMT). The cIMT can be measured noninvasively by ultrasonography (O'Leary et al, 2002). CIMT is an established marker for subclinical atherosclerosis and an independent predictor for cardiovascular risk (van den Oord et al, 2013). Whether the cIMT is associated with depression remains to be elucidated as both positive (Tiemeier et al, 2004; Elovainio et al, 2005) and negative results (Ohiraa et al, 2012) have been reported. One may hypothesize that this association only exists with specific depressive symptom profiles, which may not be assessed properly or masked in some studies.

The metabolic syndrome (central adiposity, abnormal glucose regulation, elevated triglycerides, lowered high-density lipoprotein cholesterol and elevated blood pressure) (Alberti et al, 2009) is associated with subclinical atherosclerosis in young, middle-aged and older adults (Hulthe et al, 2000; Kullo et al, 2005; Tzou et al, 2005; Bertoni et al, 2007; Chirinos et al, 2014). There is an association between depression and the metabolic syndrome (Koponen et al, 2008; Akbaraly et al, 2011; Pan et al, 2012) as well as with its individual components like impaired glycemic control (Gale et al, 2010). Waist circumference seems the most important metabolic syndrome feature in relation to depression in older persons (Vogelzangs et al, 2011). Meta-analysis of cross-sectional studies confirmed a significant association between depression and body mass index as index for obesity (de Wit et al, 2010) and meta-analyses of longitudinal studies found depression as a risk factor for weight gain, as well as body mass index as a risk factor for the development of depression (Luppino et al, 2010). Obesity as risk factor for clinical cardiovascular diseases, however, seems specifically related to anthropometric measures of abdominal adiposity, such as waist hip-ratio (WHR) and waist circumference (Yan et al, 2009). Atherosclerotic progression is accelerated by abdominal obesity (Yan et

al, 2009; Chagas et al 2011). A likely explanation lies in the fact that visceral fat is metabolically active by the secretion of inflammatory cytokines, collectively called adipokines.

Neuroticism

Apart from cardiovascular disease (Taylor et al, 2013; Valkanova et al, 2013), neuroticism is also a major vulnerability factor in late-life depression (Steunenberg et al, 2006; Kendler at al, 2006). Neuroticism refers to the personality trait of being sensitive to negative stimuli (Tellegen et al, 1985), causing emotional instability and negative moods like anxiety, sadness, guilt, hostility and self-dissatisfaction (Watson & Clark, 1984; Steunenberg et al, 2007). In depression, the cognitive-affective symptoms, like worrying or suicidal thoughts, may be more specifically associated with neuroticism. Cognitive reactivity (i.e. the ease with which particular patterns of negative thinking are reactivated in response to low mood) mediates the predisposing effects of neuroticism to depression (Barnhofer et al, 2010; Boyle et al, 2010). The typical or melancholical depression subtype is characterized by a combination of stressful life events and vulnerability of personality characteristics in the domains of neuroticism and stress sensitivity (Kendler at al, 2002; Ormel et al, 2001; Ormel et al, 2004; Hettema et, al 2006).

Neuroticism is one of the most well established dimensions in the 'Big Five' (Costa & McCrae, 1994) and is strongly related to mental and physical health, level of social support, self-rated health and functional limitations (Siegler & Brummet, 2000; Smith & Gallo, 2001; Duberstein et al, 2003). In line with the stability assumption (Costa & McCrae, 1994; Costa et al, 2000; Martin et al, 2002; Maiden et al, 2003), neuroticism remains rather stable in old age and is independent of physical illness and functional limitations (Steunenberg et al, 2005). A higher level of neuroticism predicts chronicity of depression in later life with an effect-size comparable to the negative impact of physical health and even stronger than the negative impact of cognitive decline or loss of social resources (Steunenberg et al, 2007). Finally, a high level of neuroticism is a strong predictor of recurrence (Surtees et al, 1996; Steunenberg et al, 2009; Steunenberg et al, 2010). In this thesis, the interaction between vascular disease burden and neuroticism will be explored, taking depressive symptom profiles into account.

Towards integration of subclinical vascular disease, neuroticism and depressive symptom profiles

Recently an integrative model of the relationships between depression and the prognosis of coronary artery disease (CAD) was postulated (Ormel & de Jonge, 2011). The model

hypothesizes that CAD, with its underlying atherosclerosis, is a risk factor for somatic-affective depression but less so for cognitive-affective depression. This hypothesis is primarily based on findings with the Beck Depression Inventory (BDI) for which two dimensions are found consistently in depressed cardiac patients (a cognitive-affective and a somatic-affective dimension) and less consistently a third dimension (appetitive) (de Jonge et al, 2006; Linke et al, 2009). Subclinical atherosclerosis might affect the risk of somatic depression by the involvement of systemic inflammation (Frasure et al, 2007; Glassmann et al, 2007) long before the diagnosis of CAD. In a large sample of older primary care patients initially free of CAD diagnosis it was found that the longitudinal relationship between overall depressive symptom severity and incident CAD events might be driven primarily by the somatic symptom dimension of depression (Hawkins et al, 2014).
Neuroticism and cardiovascular disease, as major risk factors for late-life depression, have hardly been examined in relation to each other. A small case-control study found a negative interaction between vascular risk and psychosocial vulnerability for depression (Oldehinkel et al, 2003). In older people aged 70 years and older, the effect of neuroticism on explaining depressive symptoms was attenuated by the presence of cerebrovascular disease (Wouts et al, 2011).

Two aspects will be elaborated in the present thesis.

- Firstly, based on the above, a hypothesis may be that depressive symptoms, especially the somatic-affective symptoms, may simply be symptoms of an underlying somatic disorder. This may explain why subthreshold forms of depression, often consisting of primarily somatic-affective symptoms, are related to negative health outcomes.
- Secondly, although the findings in literature till so far about the interaction between neuroticism and cardiovascular disease may have been chance findings or ceiling effects of two important risk factors, one also may hypothesize that cerebrovascular disease causes apathy that in turn decreases the effect of neuroticism on depression. Cerebrovascular damage leads to fronto-striatal dysfunction and neuropsychological deficits, especially decreased processing speed and executive dysfunctioning, that are more specifically linked with apathy than with depressed mood per se. This apathy may lead to less impact of neuroticism on late life depression.

Both of these hypotheses will be explored in this thesis. Before we do so, a few case reports will be presented that illustrate the clinical relevance of these questions.

Some case-reports

Case description A
Mr A, a 68-year-old man was seen in consultancy because of depressive symptoms and inactivity. The patient had developed a non-fatal stroke and a diagnostic workup by the neurologist showed a serious degree of subclinical atherosclerosis, even without clinical vascular disease in history. His medical history reported one depressive period prior to the non-fatal stroke but no cardiac or cerebrovascular disease. He suffered from the first episode of a major depressive disorder three years ago in the absence of either precipitating circumstances as predisposing characteristics. He did not report any life-event prior to this episode and there was no evidence of instable personality traits. He said to be happily married, to be father of three successful children and to have enjoyed two years of his retirement after a satisfying job as a construction worker. The general practitioner had treated his depression successfully with paroxetine combined with some sessions of problem solving therapy. To the patient's opinion the depressive symptoms were fully in remission after treatment. His wife, however, was not fully convinced, as symptoms of 'fatigue' existed and he did not enjoy sea fishing with his friends anymore. Psychiatric examination showed a moderate depressed mood, reduced initiative, psychomotor retardation and signs of executive deficits.

Should we conclude there was a recurrence of a depressive episode? Could the occurrence of his first depression have been the first marker of his vascular disease burden? Would this possibility have warranted a vascular check-up in this case?

Case description B
Mrs B, a 70-year-old woman was admitted at the emergency ward of old-age psychiatry with the diagnoses of Major Depressive Disorder. She had a history of recurrent depressive disorder. From her 26th till 59th she had been admitted four times. Always there had been precipitating circumstances (birth of a child, loss of her mother, moving to another part of the country, worrying about her children). During the admissions a recurrent depressive disorder in a woman with neurotic personality traits was diagnosed. The major depressive episodes always remitted fully by a tricyclic antidepressant (amitriptyline or nortriptyline) in combination with cognitive therapy. Beside her psychiatric history there was no somatic history except backache and headache without a somatic explanation and at the age of 57 she developed hypertension. Because of this diagnosis of hypertension, she quit smoking.

Before the current admission there were no precipitating circumstances. In fact, according to her husband and children, she had been less worrisome and anxious during the last decade. She had continued using nortriptyline, prescribed by the general practitioner. In the last year she developed more depressive symptoms. She was tired, lost appetite and weight; she became dramatically preoccupied with physical sensations and developed insomnia. The weeks before submission she was sad, cried a lot and was very irritated towards her husband. Psychiatric examination suggested a depressed mood and decreased speed in thinking. She was preoccupied by her somatic complaints. Physical and laboratory tests revealed no abnormalities. The Montgomery Asberg Depression Rating Scale (MADRS) score was 30. A Major Depressive Disorder was diagnosed. During admission cognitive therapy was restarted and the nortriptyline level appeared not be adequate, so the dosage was elevated to get an optimal level. After 6 weeks there was no remission; addition of lithiumcarbonate in adequate dosage also had no effect.

How can we explain that this episode occurred without precipitating events and why did she not recover after optimising the drug therapy that had previously and repeatedly been successful?

Case description C
Mr C, a 55-year-old man, was referred by the GP because of a depression. His psychiatric history included a posttraumatic stress disorder after a car accident, which has been successfully treated with Eye-Movement Desensitisation Reprocessing (EMDR). His somatic history was limited to diabetes mellitus type 2 and hypertension. The daughter was psychiatrist herself and advised her father to see a colleague psychiatrist because she doubted the GPs diagnosis of depression.

Mr C himself did not have many complaints. He felt a little bit fatigue but reported to be still socially involved. Nonetheless, he was taking more rest at home, which has resulted in conflicts with his wife because of his inactivity. Feelings of guilt were only present when his wife confronted him with his inactivity. He was happily married although his wife became frustrated by the depressive symptoms of Mr C. Until 8 months ago he worked as a teacher on a primary school in the village where he lives. He had always been a popular man in the village; beside his work he was active in the musical society where he plays tuba. The last year, he increasingly skipped his weekly meetings without any apparent reasons. This was obvious to his wife because Mr C always liked the social aspects of the meeting, talking to other musicians and sharing a drink.
Psychiatric examination revealed inactivity, some slowness in thinking and a dysphoric

mood. Physical examination showed beside a hypertension of 170/100 mmHg and an obvious potbelly with a waist circumference of 125 cm, no abnormalities. Laboratory tests only showed elevated triglycerides. As medication he used fosinopril, metformin and simvastatin.

Is Mr C indeed suffering from a late-life depression? Or was the presumption of his daughter right and does Mr C suffer from a specific subtype of late-life depression, i.e. a 'metabolic depression with prominent somatic-affective depressive symptoms and few cognitive-affective symptoms'? Or does Mr C suffer from apathy?

Case description D
Miss D, an 84-year-old woman was seen in a nursery by a consultant psychiatrist. After an operation for hip-fracture and admission at a geriatric traumatology ward, she was referred to the nursery. The psychiatric history showed a depression at the age of 23 after a girl friend had committed suicide. She had been physically healthy all of her life.

The reason for consultation was that the rehabilitation was not going well because she refused to cooperate with the nurses and physiotherapist. To the nurses, miss D appeared to be exhausted, but her doctor found no explanation for this in physical and laboratory tests. Miss D complained about sadness, worrying about the future, loss of appetite, weight loss during the last 8 months and insomnia. Her nephew mentioned that miss D has always been an active woman. She has never been married and worked as a tour guide in Asia and Africa. After retirement she did some work as a local tour guide in the city centre. She was a great aunt for all her nephews and nieces, a very social woman. She visited her family often, loved knitting and stitching, gardening and played bridge. In fact she was active till Christmas two years ago, when she increasingly worried about recently emerged family conflicts. She became more and more inactive, lost weight, felt very weak and fell at least twice a month without a reason. It was very frustrating for her to become dependent. In psychiatric examination an underweight woman was seen with an obvious slowness and indeed she made an exhausted impression. She was preoccupied with guilt and frustration about her dependency. She was dissatisfied with the admission in the nursery; there was no future for her. The mood was extremely sad.

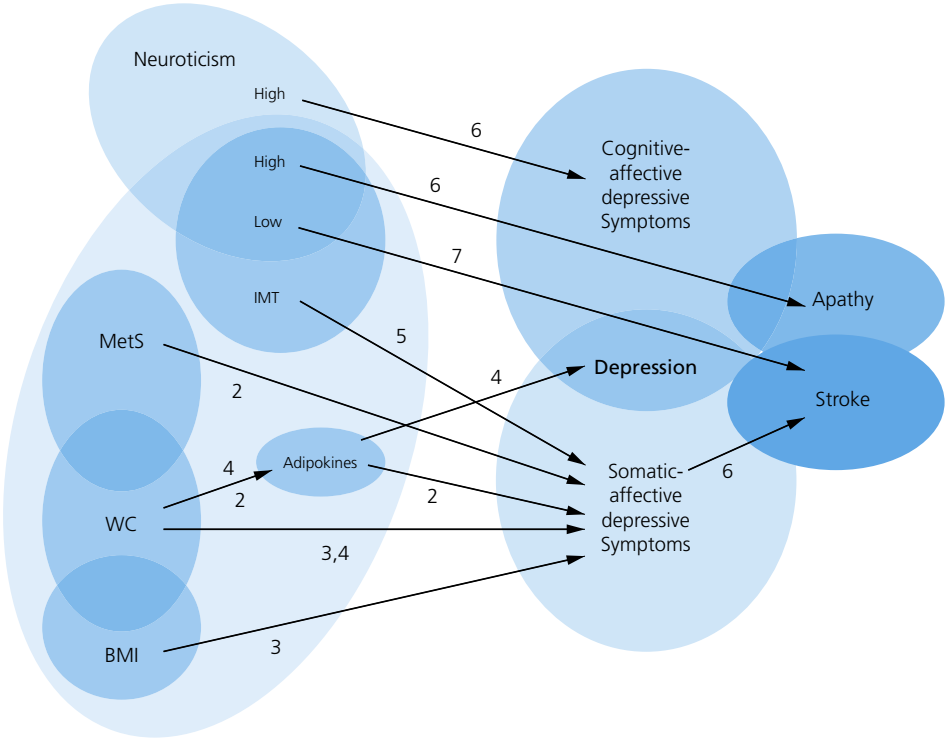
Is this a classical normal depression? Should we expect a specific profile in a frail older woman?

Aims and outline of this thesis

The main aim of this thesis is to study the association between the late-life depression and subclinical vascular disease, taking into account different depressive symptom profiles and neuroticism. More specifically, we formulated the following hypotheses:

1. Subclinical vascular disease is associated with late-life depression:
   a. Metabolic syndrome is associated with late-life depression
   b. Obesity is associated with late-life depression
   c. Generalised atherosclerosis indexed by the intima media thickness (IMT) of the carotid artery is associated with late-life depression
2. Subclinical vascular disease, more specifically metabolic syndrome, obesity and IMT are particularly associated with the somatic-affective symptom cluster in depression.
3. (Subclinical) vascular disease and neuroticism represent two different etiological pathways in late-life depression.

Figure 1 Associations tested in this thesis (numbers refer to chapter numbers).



Part one: Metabolic syndrome and obesity

Part one of this thesis focuses on the association between depressive symptom profiles and metabolic syndrome. Particular attention is paid to the abdominal obesity as central component of the metabolic syndrome and its metabolic activity.

In chapter 2 we describe the association between the metabolic syndrome and its individual components and depressive symptoms using baseline data of the Nijmegen Biomedical Study (NBS). The associations are studied in middle aged and older persons (50 - 70 years) living in the community. One important limitation of previous studies on the association between the metabolic syndrome and late-life depression is examined in more depth, namely the subtyping of depressive symptoms, including somatic-affective symptom cluster and cognitive-affective symptom cluster based on the Beck Depression Inventory. As visceral fat tissue is metabolically active by the secretion of cytokines, as mentioned before collective called adipokines, which may contribute to the negative health effect of obesity. We will explore the association between depression and adiponectin, as this has been linked to mood regulation, although results are mixed (Lehto et al, 2010; Diniz et al, 2012; Jeong et al, 2012). In contrast to other adipokines, adiponectin is a protective cytokine for vascular health and lowered concentration have been demonstrated in visceral obesity, insulin resistance, diabetes mellitus, metabolic syndrome and hypertension independent of the body mass index (Mathieu et al, 2009; Taylor et al, 2010; Zeugmann et al, 2010; Matsuzawa et al, 2011; Yadav et al, 2012).

In chapter 3 we will focus on probably the most important component of the metabolic syndrome in the association with depression, obesity. Two important limitations of previous studies on the association between obesity and late-life depression are examined in more depth. First, the use of different measures of obesity, including Body Mass Index, Waist-Hip ratio and waist circumference. Secondly, the subtyping of depressive symptoms, including somatic-affective symptom cluster and cognitive-affective symptom cluster based on the Beck Depression Inventory.

Chapter 4 addresses the association between late-life depression and waist-circumference in an older (≥60 years) clinically depressed sample from the Netherlands Study of Depression in Older persons (NESDO). This enabled us to explore several characteristics of late-life depression like age of onset, comorbidity with dysthymia and duration of illness in addition to symptom profiles based on the Inventory of Depressive Symptoms in the association between depression and obesity. In this paper, we also examine the role of Neutrophil Gelatinase-Associated Lipocalin (NGAL), an inflammatory marker recently identified as an adipokine (Huang et al, 2012).

Part two: Atherosclerosis and neuroticism

In part two we focus on (subclinical) atherosclerosis and neuroticism as two of the major risk factors of late-depression.

In chapter 5, we first describe a study into the relationship between (subclinical) atherosclerosis, measured by the intima media thickness (IMT), and depressive symptom clusters within the Nijmegen Biomedical Study (NBS). Hereby, we extend previous studies showing an association between atherosclerosis and depression in general. In chapter 6, we further explore these associations by examining the interaction between subclinical atherosclerosis and neuroticism with regard to explaining variance in both somatic-affective depressive symptoms and cognitive-affective depressive symptoms.

Finally, in chapter 7, neuroticism and vascular disease are examined in a community sample age 55 years and over taken from the Longitudinal Aging Study Amsterdam (LASA). The findings in chapter 5 and 6 culminate in the hypothesis that two separate groups of patients with late-life depression can be discerned based on aetiological ground, a neuroticism-associated and vascular depression. We hypothesise that patients with subclinical vascular disease are at increased risk for stroke, whereas those suffering from neuroticism-associated depression are not. Therefore we will examine whether or not subjects with low levels of neuroticism do indeed have an increased risk of stroke in patients free of vascular events.

In chapter 8 the main findings of these studies are reviewed, methodological considerations and the clinical implications for the elderly depressed patients are discussed.

Appendix

In this thesis, three different data sets were used derived from three studies: two population based studies and one clinical cohort study including patients suffering from late-life depressive disorders.

Nijmegen Biomedical Study (NBS)

The Nijmegen Biomedical Study is a population-based survey conducted in Nijmegen of people aged 20-90 years. In the year 2000 the NBS was initiated among the inhabitants of the municipality of Nijmegen by the departments of Epidemiology, Biostatistics and HTA, Clinical Chemistry, and Endocrinology of the Radboud University Nijmegen Medical Centre (RUNMC). Age- and sex-stratified randomly selected adult inhabitants of Nijmegen (n =22 452) received an invitation to fill out a postal questionnaire on lifestyle and medical history. A total of 9371 (41.7%) recipients responded to the questionnaire (Hoogendoorn et al, 2006; Holewijn et al, 2010).

For the studies presented in this thesis a sample was drawn from the NBS. In 2004 and 2005 a questionnaire was sent to all participants (N=2807) aged 50 to 70. Of these persons 1517 (54%) gave additional informed consent to participate in a study on non-invasive measurement of atherosclerosis. These participants visited the hospital for a detailed assessment of atherosclerotic disease and its risk factors and consequences.

Netherlands Study of Depression in Older Persons (NESDO)

The Netherlands Study of Depression in Older Persons (NESDO) is a multi-site naturalistic cohort study, aims to examine the course and consequences of depressive disorders in older persons. From 2007 until 2010 the NESDO consortium has recruited 378 depressed and 132 non-depressed older persons aged 60 through 93 years. Recruitment of depressed older persons took place at five regions in the Netherlands from both mental health care institutes and general practitioners in order to include persons with late-life depression in various developmental and severity stages. The comparison group of non-depressed persons was recruited at the same general practices that recruited patients. A random sample of older people who scored less than four on the Geriatric Depression Scale during a visit to their GP was asked informed consent. (Comijs et al, 2011)

For the present study we used the baseline assessment of the NESDO. The baseline assessment included written questionnaires, interviews, a medical examination, cognitive tests and collection of blood and saliva samples. Information was gathered about mental health outcomes and demographic, psychosocial, biological, cognitive and genetic determinants.

Longitudinal Aging Study Amsterdam (LASA)

The Longitudinal Aging Study Amsterdam is a prospective cohort study of Dutch people aged 55 to 85 years (n=3107). LASA started in 1992 and the general aim of LASA was to study the autonomy and well-being of an aging population. A randomly selected age- and sex-stratified sample (according to expected mortality figures) was drawn from the population registers of 11 municipalities in the Netherlands. The reason for this relative oversampling of men and oldest-old people (both men and women) was to compensate for an anticipated higher unavailability for follow-up among the older-old and men. The sample first took part in the cross-sectional NESTOR–living arrangements and social networks study and was later interviewed and followed up every 3 years in LASA. Of the NESTOR–living arrangements and social networks study sample, 81.7% of the persons also participated in LASA (non-response was related to age but not to sex). All interviews were tape-recorded for quality control purposes. (Beekman et al, 1995; Huisman et al, 2011).

For the study presented in this thesis, we used data up to 9 years of follow-up and included only those LASA participants, in whom neuroticism was evaluated at baseline, leaving a total study sample of 2050 participants.

References

Aben I, Denollet J, Lousberg R et al. (2002) Personality and vulnerability to depression in stroke patients: a 1-year prospective follow-up study. *Stroke;* 33(10):2391-2395.

Alberti KG, Eckel RH, Grundy SM et al. (2009) Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung and Blood Institute; American Heart Associatioin; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation;* 120:1640-1645

Alexopoulos GS, Meyers BS, Young RC et al. (1997) 'Vascular Depression' hypothesis. *Arch Gen Psychiatry;* 54(10):915-922.

Alexopoulos GS. (2001) 'The Depression-Executive Dysfunction Syndrome of Late Life': a specific target for D3 agonists? *Am J Geriatr Psychiatry;* 9:22-29.

Akbaraly TN, Ancelin ML, Jaussent I et al. (2011) Metabolic syndrome and onset of depressive symptoms in the elderly. *Diabetes Care;* 34 (4):904-909.

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. (2001) 4th edn American Psychiatric Association: Washington, DC, USA.

Baldwin RC. (2005) Is vascular depression a distinct sub-type of depressive disorder? A review of causal evidence. *Int J Geriatr Psychiatry;* 20:1e11.

Barnhofer T, Chittka T. (2010) Cognitive reactivity mediates the relationship between neuroticism and depression. *Beh Res Ther;* 48:275e281.

Bech P, Allerup P, Gram LF et al. (1981) The Hamiilton Depression Scale. Evaluation of objectivity using logistic models. *Acta Psychiatrica Scandinavia;* 63:290-299.

Beck AT, Steer RA. (1987) Manual for the Revised Beck Depression Inventory 1. San Antonio, Tex, *Psychological corporation.*

Beekman AT, Deeg DJH, van Tilburg T et al. (1995) Major and minor depression in later life: a study of prevalence and risk factors. *J Affect Disord;* 36:65-75.

Beekman AT, Copeland JR, Prince MJ. (1999) Review of community prevalence of depression in later life. *Br J Psychiatry;* 174:307-311.

Beekman ATF, Geerlings SW, Deeg DJH et al. (2002) The natural history of late-life depression. A 6-year prospective study in the community. *Arch Gen Psychiatry;* 59:605-611.

Bertoni AG, Wong ND, Shea S et al. (2007) Insulin resistance, metabolic syndrome, and subclinical atherosclerosis: The Multi-Ethnic Study of Atherosclerosis (MESA). *Diabetes Care;* 30:2951-2956.

Boyle LL, Lyness JM, Duberstein PR et al. (2010) Trait neuroticim, depression, and cognitive function in older primary care patients. *Am J Geriatr Psychiatry;* 18:305e312.

Chagas P, Caramori P, Barcellos C et al. (2001) Association of different anthropometric measures and indices with coronary atherosclerotic burden. *Arquivos Brasileiros De Cardiologica;* 97 (5): 397-401.

Chirinos DA, Medina-Lezama J, Arguelles W et al. (2014) Metabolic syndrome as an underlying

disease entity and its relationship to subclinical atherosclerosis in andean hispanics. *Metab Syndr Relat Disord;* 12(1):49-55.

Coffey CE, Figiel GS, Djang WT et al. (1989) White matter hyperintensities on magnetic resonance imaging: clinical and anatomic correlates in the depressed elderly. *J Neuropsychiatry Clin Neurosci;* 1:135-144.

Comijs, HC, van Marwijk HW, van der Mast RC et al. (2011) The Netherlands study of depression in older persons (NESDO); a prospective cohort study. *BMC Researc Notes 4;* 524.

Costa PT, McCrae RR (1994) The stability of personality: observations and evaluations. *Current Directions in Psychological Science;* 3:173-175.

Costa, PT, McCrae RR. Ostendorf F et al. (2000) Nature over nurture: Temperament, personality, and life span development. *Journal of Personality and Social Psychology;* 78:173-186.

Dalby RB, Chakravarty MM, Ahdidan J et al. (2010) Localization of white-matter lesions and effect of vascular risk factors in late onset major depression. *Psychol Med;* 40:1389-1399.

Diniz BS, Teixeira AL, Campos AC et al. (2012) Reduced serum levels of adiponectin in elderly patients with major depression. *J Psychiatr Res;* 46(8):1081-5.

Dombrovski AY, Mulsant BH, Houck PR et al. (2007) Residual symptoms and recurrence during maintance treatment of late-life depression. *J Affect Disord;* 103:77-82.

Duberstein PR, Sorensen S, Lyness JM et al. (2003) Personality is associated with perceived health and functional status in older primary care patients. *Psychology and Aging;* 18:25-37.

Elovainio M, Keltikangas-Jarvinen L, Kivimaki M et al. (2005) Depressive symptoms and carotid artery intima-media thickness in young adults : the Cardiovascular Risk in Young Finns Study. *Psychosomatic Medicine;* 67:561–567.

Esposito F, Rochat L, Juillerat Van der Linden AC et al. (2010) Apathy and executive dysfunction in Alzheimer disease. *Alzheimer dis Assoc Disord;* 24(2): 131-137

Fiske A, Wetherell JL, Gatz M. (2009) Depression in older adults. *Annu. Rev. Clin. Psychol*; 5:363-389.

Gale CR, Kivimaki M, Lawlor DA et al. (2010) Fasting Glucose, Diagnosis of Type 2 Diabetes and Depression: the Vietnam Experience Study. *Biol Psychiatry;* 67:189-192.

Frasure-Smith N, Lesperance F, Irwin MR et al. (2007) Depression, C-reactive protein and two-year major adverse cardiac events in men after acute coronary syndromes. *Biol Psychiatry;* 62:302-308

Glassman AH, Miller GE. (2007) Where there is depression, there is inflammation sometimes! *Biol Psychiatry;* 62:280-281.

Goodman J, Shimbo D, Haas DC et al. (2008) Incident and recurrent major depressive disorder and coronary artery disease secerity in acute coronary syndrome patients. *Journal of Psychiatric Research;* 42:670-675.

Hawkins MA, Callahan CM, Stump TE et al. (2014) Depressive symptom clusters as predictors of incident coronary artery disease: a 15-year prospective study. *Psychosomatic medicine;* 76:38-43.

Hegeman JM, Wardenaar KJ, Comijs HC et al. (2012) The subscale structure of the Inventory of

Depressive Symptomatology Self Report (IDS-SR) in older persons. *Journal of Psychiatric Research; 46:*1383-1388.

Hettema JM, Neale MC, Myers JM et al. (2006) A population-based twin study of the relationship between neuroticism and internalizing disorders. *Am J Psychiatry;* 163:857-864.

Holewijn S, den Heijer M, van Tits LJ et al. (2010) Impact of waist circumference versus adiponectin level on subclinical atherosclerosis. *J Intern Med ;* 267:588-598.

Hoogendoorn EH, Hermus AR, de Vegt F et al. (2006) Thyroid function and prevalence of anti-thyroperoxidase antibodies in a population with borderline sufficient iodine intake: Influences of age and sex. *Clin Chem;* 52:104-111.

Huang Y, Yang Z, Ye Z et al. (2012) Lipocalin-2, glucose metabolism and chronic low-grade systemic inflammation in Chinese people. *Cardiovascular Diabetology;* 11:11-18.

Huisman M, Poppelaars J, van der Horst M et al. (2011) Cohort Profile: The Longitudinal Aging Study Amsterdam. *Int J Epidemiol;* 40(4):868-76.

Hulthe J, Bokemark L, Wikstrand J et al. (2010) The metabolic syndrome, LDL particle size and atherosclerosis: the Atherosclerosis and Insulin Resistance (AIR) study. *Arterioscler Thromb Vasc Biolo;* 20:2140-7.

Jeong HC, Jun Min B, Lim S et al. (2012) Plasma Adiponectin elevation in elderly individuals with subsyndromal depression. *Psychoneuroendocinology;* 37:948-955.

de Jonge P, Ormel J, van den Brink RH et al. (2006) Symptom dimensions of depression following myocardial infarction and their relationship with somatic health status and cardiovascular prognosis. *Am J Psychiatry;* 163(1):138-144.

Katon WJ, Lin E, Russo J et al. (2003) Increased medical costs of a population-based sample of depressed elderly patients. *Arch Gen Psychiatry;* 60:897-903.

Kendler KS, Gardner CO, Prescott CA. (2002) Toward a comprehensive developmental model for major depression in women. *Am J Psychiatry;* 159:1133-1145.

Kendler KS, Gatz M, Gardner CO et al. (2006) Personality and major depression: a Swedish longitudinal, population-based twin study. *Arch Gen Psychiatry;* 63(10):1113–1120.

Koponen H, Jokelainen J, Keinanen-Kiukaanniemi S et al. (2008) Metabolic syndrome predisposes to depressive symptoms: a population-based 7-year follow-up study. *J Clin Psychiatry;* 69(2):178-82.

Krishnan KR, Hays JC, Blazer DG. (1997) MRI-defined vascular depression. *Am J Psychiatry;* 154(4):497-501.

Kullo IJ, Cassidy AE, Peyser PA et al. (2004) Association between metabolic syndrome and subclinical coronary atherosclerosis in asymptomatic adults. *Am J Cardiol;* 94:1554-1558.

Lehto SM, Huotari A, Niskanen L et al. (2010) Serum adiponectin and resistin levels in major depressive disorder. *Acta Psychiatr Scand;* 121(2):209-15.

Lenze EJ, Schulz R, Martire LM et al. (2005) The course of functional decline in older people with persistently elevated depressive symptoms: Longitudinal findings from the Cardiovascular

Health Study. *JAGS;* 53:569-575.

Licht-Strunk E, van der Windt DA, van Marwijk HW et al. (2007) The prognosis of depression in older patients in general practice and the community. A systematic review. *Fam Pract;* 24(2): 168-80.

Linke SE, Rutledge T, Johnson BD et al. (2009) Depressive symptom dimensions and cardiovascular prognosis among women with suspected myocardial ischemia: a report from the National Heart, Lung, and Blood Institute-sponsored Women's Ischemia Syndrome Evaluation. *Arch Gen Psychiatry;* 66:499-507.

Luppa M, Heinrich S, Matschinger H et al. (2008) Direct costs associated with depression in old age in Germany. *J Affect Disord;* 105:195-204.

Luppa M, Sikorski C, Luck T et al. (2012) Age- and gender-specific prevalence of depression in latest-life – Systematic review and meta-analysis. *J Affect Disord;* 136:212- 221.

Luppino FS, de Wit LM, Bouvy PF et al. (2010) Overweight, obesity and depression. A systemic review and meta-analysis of longitudinal studies. *Archives General Psychiatry;* 67:220-229.

Maiden RJ, Peterson SA, Caya M et al. (2003) Personality changes in the old-old: a longitudinal study. *Journal of Adult Development;* 10 (1):31-39.

Martin P, Long M, Poon LW. (2002) Age change and differences in personality traits and states of the old and very old. *Journal of Gerontology: Psychological Sciences;* 57B (2):144-152.

Mast BT, Miles T, Penninx BW et al. (2008) Vascular disease and future risk of depressive symptomatology in older adults: findings from the health, aging, and body composition study. *Biol Psychiatry;* 64:320-326.

Mathieu P, Poirier P, Pibarot P et al. (2009) Visceral Obesity: the link among inflammation, hypertension and cardiovascular disease. *Hypertension;* 53:577-584.

Matsuzamwa Y, Funahashi T, Nakamura. (2011) The concept of metabolic syndrome; contribution of visceral fat accumulation and its molecular mechanism. *J Atheroscler Thromb;* 18:629-639.

Morley S, Williams AC, Black S. (2002) A confirmatory factor analysis of the Beck Depression Inventory in chronic pain. *Pain;* 99:289-298

Mueller TI, Kohn R, Leventhal N et al. (2004) The course of depression in elderly patients. *Am J Geriatr Psyhiatry;* 12(1):22-9.

Pan A, Keum N, Okereke OI et al. (2012) Bidirectional association between depression and metabolic syndrome. *Diabetes;* 35:1171-1180.

Pancheri P, Picardi A, Pasquini M et al. (2002) Psychopathological dimensions of depression: a factor study of the 17-item Hamilton depression rating scale in unipolar depressed outpatient. *J Affect Disord;* 68:41-47.

Penninx BWJH, Milaneshi Y, Lamers F et al. (2013) Understanding the somatic consequences of depression: biological mecahnisms and the role of depression symptom profile. *BMC Medicine;* 11: 129. Doi: 10.1186/1741-7015-11-129.

O'Leary DH, Polak JF. (2002) Intima-media thickness: a tool for atherosclerosis imaging and event

prediction. *Am J Cardiol;* 90(10C):18-21.

Ohiraa R, Diez Roux AV, Polak JF et al. (2012) Associations of anger, anxiety and depressive symptoms with carotid arterial wall thickness: the multi-ethnic study of atherosclerosis. *Psychosomatic Medicine;* 74:517-525.

Oldehinkel AJ, Ormel J, Brilman EI et al. (2003) Psychosocial and vascular risk factors of depression in later life. *J Affect Disord;* 74:237-246.

Ormel J, Oldehinkel AJ, Brilman EI. (2001) The interplay and etiological continuity of neuroticism, difficulties and life events in the etiology of major and subsyndromal, first and recurrent depressive episodes in later life. *Am J Psychiatry;* 158:885-891.

Ormel J, Oldehinkel AJ, Vollebergh W. (2004) Vulnerability before, during, and after a major depressive episode: a 3-wave populationbased study. *Arch Gen Psychiatry;* 61:990-996.

Ormel J, de Jonge P. (2011) Unipolar depression and the progression of coronary artery disease: toward an integrative model. *Psychother Psychosom;* 80:264-274.

Penninx BWJH, Milaneschi Y, Lamers F et al. (2013) Understanding the somatic consequences of depression: biological mechanisms and the role of depression symptom profile. *BMC Medicine;* 1: 129-143.

Riedel-Heller SG, Busse A, Angermeyer MC. (2006) The state of mental health in old-age across the 'old' European Union– a systematic review. *Acta Psychiatr Scand;* 113:388-401.

Ross. (1993) The pathogenesis of atherosclerosis: a perspective for the 1990s. *Nature;* 362:801-809.

Rush AAJ, Gullion CM, Basco MR et al. (1996) The Inventory of Depressive Symptomatology (IDS): psychometric properties. *Psychological Medicine;* 26:477-486.

Shafer AB. (2006) Meta-analysis of the factor structures of four depression questionnaires: Beck, CES-D, Hamilton, and Zung. *J Clin Psychol;* 62:123-146.

Siegler IC & Brummett BH. (2000) Associations among NEOpersonality assessments and well-being at midlife: Facet-level analyses. *Psychology and Aging;* 15:710-714.

Sheline YI, Price JL, Vaishnavi SN et al. (2008) Regional white matter hyperintensity burden in automated segmentation distinguishes late-life depressed subjects from comparison subjects matched for vascular risk factors. *Am J Psychiatry;* 165:524-532.

Smith TW, & Gallo LC. (2001) Personality traits as risk factors for physical illness. In A. Baum, T. Revenson, & J. Singer (Eds.), Handbook of health psychology (139-172). Hillsdale, NJ: Erlbaum

Smith EE, Salat DH, Jeng J et al. (2011) Correlations between MRI white matter lesion location and executive function and episodic memory. *Neurology;* 76:1492-1499.

Sneed JR, Rindskopf D, Steffens DC et al. (2008) The vascular depression subtype: evidence of internal validity. *Biol Psychiatry;* 64:491-497.

Stek ML, Vinkers DJ, Gussekloo J et al. (2006) Natural history of depression in the oldest old. *Br J Psych;* 188:65-69.

Steunenberg B, Twisk JW, Beekman AT et al. (2005) Stability and change of neuroticism in aging.

J Gerontol B Psychol Sci Soc Sci; 60(1):27-33

Steunenberg B, Beekman AT, Deeg DJ et al. (2006) Personality and the onset of depression in late life. *J Affect Disord;* 92(2-3):243-251.

Steunenberg B, Beekman AT, Deeg AJH et al. (2007) Mastery and neuroticism predict recovery of depression in later life. *Am J Geriatr Psychiatry*; 15:234-242.

Steunenberg B, Braam AW, Beekman ATF et al. (2009) Evidence for an association of the big five personality factors with recurrence of depressive symtpoms in later life. *Int J Geriatr Psychiatry;* 24:1470-1477.

Steunenberg B, Beekman ATF, Deeg DJH et al. (2010) Personality predicts recurrence of late-life depression. *J Aff disorders;* 123:164-172.

Surtees PG, Wainwright NW. (1996) Fragile states of mind: neuroticism, vulnerability and long-term outcome of depression. *Br J Psychiatry;* 169:338-347.

Taylor WD, MacFall JR, Payne ME et al. (2005) Greater MRI lesion volumes in elderly depressed subjects than in control subjects. *Psychiatry Res;* 139:1-7.

Taylor VH, Macqueen GM. (2010) The role of adipokines in understanding the associations between obesity and depression. *J Obes;* 748048. Doi: 10.1155/2010/748048. Epub 2010 Jul 28.

Taylor WD, Zhao Z, Ashley-Koch A et al. (2011) Fiber tract-specific white matter lesion severity. Findings in late-life depression and by AGTR1 A1166C genotype. *Hum Brain Mapp;* 34:295-303.

Taylor WD, Aizenstein HJ, Alexopoulos GS. (2013) The vascular depression hypothesis: mechanisms linking vascular disease with depression. *Mol Psychiatry;* 18(9):963-74.

Tellegen A. (1985). Structures of mood and personality and their relevance to assessing anxiety, with a emphasis on self-report. *In Anxiety and the Anxiety Disorders,* Tuma AH, Maser JD (eds). Erlbaum: Hillsdale, NJ;681-706.

Tiemeier H, van Dijck W, Hofman A et al. (2004) Relationship between atherosclerosis and late-life depression; the Rotterdam Study. *Arch gen Psychiatry;* 61:369-376.

Thomas AJ, Perry R, Barber R et al. (2002) Pathological mechanisms for white matter hyperintensities in depression. *Ann NY Acad Sci;* 977:333-339.

Tzou WS, Douglas PS, Srinivasan SR et al. (2005) Increased subclinical atherosclerosis in young adults with metabolic syndrome: The Bogaluasa Heart Study. *J Am Coll Card;* 46:457-463.

Valkanova V and Ebmeier KP. (2013) Vascular risk factors and depression in later life: A systematic review and meta-analysis. *Biol Psychiatry;* 73:406-41.

Van den Oord SCH, Sijbrands EJG, ten Kate et al. (2013) Carotid intima-mediathickness for cardiovascular risk assessment: systematic review and meta-analysis. *Atherosclerosis;* 228(1): 1-11.

Vogelzangs N, Beekman AT, Boelhouwer IG et al. (2011) Metabolic depression: a chronic depressive subtype? Findings from the InCHIANTI study of older persons. *J Clin Psychiatry;* 72(5): 598-604.

Wardenaar KJ, van Veen VT, Giltay EJ et al. (2010) The structure and dimensionality of the Inventory of Depressive Symptomatology Self Report (IDS-SR) in patients with depressive disorders and healthy controls. *J Affect Disord;* 125:146-154.

Watson D, Clark LA. (1984) Negative affectivty: the disposition to experience aversive emotional status states. *Psychol Bull;* 96:465-490.

Wit de L, Luppino F, van Straten A et al. (2010) Depression and obesity: a meta-analysis of community-based studies. *Psychiatry Research;* 30;178(2):230-5.

Wouts L, Janzing JG, Lampe IK et al. (2011) The interaction between cerebrovascular disease and neuroticism in late-life depression: a cross-sectional study. *Int J Geriatr Psychiatry;* 26:702-710.

Yadav A, Kataria MA, Saini V et al. Role of leptin and adiponectin in insulin resistance. *Clin Chim Acta;* 2012 Dec 21. pii: S0009-8981(12)00577-3. doi: 10.1016/j.cca.2012.12.007. [Epub ahead of print].

Yan RT, Yan AT, Anderson TJ et al. (2009) The differential association between various anthropometric indices of obesity and subclinical atherosclerosis. *Atherosclerosis;* 207 (1):232-238.

Zeugmann S, Quante A, Heuser I et al. (2010) Inflammatory biomarkers in 70 depressed inpatients with and without the metabolic syndrome. *J Clin Psychiatry;* 71(8):1007-16.

Part one

Metabolic syndrome and obesity

Association between metabolic syndrome and depressive symptom profiles; a role for adiponectin?

Published with minor adaptations

Association between metabolic syndrome and depressive symptom profiles - Sex-specific?

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Abstract

Background – The association between depression and metabolic syndrome is becoming more obvious. Waist circumference (WC) might be the most important metabolic syndrome (MetS) feature in relation to late-life depression, with a possible mediating role for adiponectin.

Methods – Cross-sectional population based survey, part of Nijmegen Biomedical Study; 1277 participants (50-70 years). We measured all components of MetS, plasma adiponectin levels and depressive symptoms using Beck Depression Inventory (BDI). Using two factors derived from BDI-items by principal component analysis, representing a cognitive-affective and a somatic-affective symptom cluster, were conducted multiple regression analyses for each component of metabolic syndrome. Separate models testing BDI sum score and both depressive symptom clusters as dependent variables, respectively, were used. We explored sex-differences as well as a hypothesised mediating effect of adiponectin.

Results – The presence of MetS as well as number of metabolic risk factors were significantly associated with BDI sum score. In men WC, triglycerides and HDL cholesterol explained variance in depressive symptoms, whereas in women this effect was confined to WC. Moreover, irrespective of sex, all associations were primarily driven by the somatic–affective symptom-cluster. Adiponectin neither mediated nor moderated any of the associations found.

Conclusions – Although pathophysiological mechanisms underlying the association between metabolic disturbances and depression remains to be elucidated, our study points to sex-differences as well as a specific phenotype of depression that is associated with metabolic disturbances.

Keywords

Depression, Metabolic Syndrome X, Aged, Adiponectin

Introduction

The metabolic syndrome, defined as a cluster of cardiovascular risk factors, predicts future vascular events. Several studies have also found associations between depression and the metabolic syndrome (Koponen et al, 2008; Akbaraly et al, 2011; Pan et al, 2012) as well as with its individual components like impaired glycemic control (Gale et al, 2010). Recently, the concept of 'metabolic depression' has been proposed based on findings of an increased incidence of late-life depression in persons with the metabolic syndrome as well as a protracted course of depression in depressed patients who also have metabolic syndrome characteristics (Vogelzangs et al, 2011). The chronic form of the atypical depression is associated with inflammatory and metabolic dysregulation while the chronic form of the melancholic depression is associated with hypothalamic-pituitary-adrenal (HPA)-axis hyperactivity (Lamers et al, 2012). Waist circumference seems the most important metabolic syndrome feature in relation to depression (Vogelzangs et al, 2011). Longitudinal studies have indeed confirmed a reciprocal relationship between depression and obesity (Vogelzangs et al, 2008; Luppino et al, 2010; Pan et al, 2012). Recently, the predictive value of obesity for the onset of depression appeared to be partly dependent on metabolic health (Hamer et al, 2012).

Some aspects of the association between the metabolic syndrome and depression, however, need further clarification, in particular the heterogeneity of depression and the metabolic activity of adipose tissue.

Firstly, depressive disorder is a heterogeneous syndrome. Accumulating evidence shows that the somatic-affective symptom cluster of depression is particularly related to vascular health (de Jonge et al, 2006; Roest et al, 2011). Similarly, somatic-affective in contrast to cognitive-affective symptoms, are associated specifically with waist circumference but not with body mass index (Marijnissen et al, 2011). Other components of the metabolic syndrome have not been examined in relation to depressive symptom profiles.

Secondly, visceral fat tissue is metabolically active by the secretion of cytokines, among which leptin, resistin and adiponectin, collectively called the adipokines. In older men, high leptin levels are associated with an increased onset of depressive symptoms especially in the presence of abdominal obesity (Milaneshi et al, 2012). In contrast to other adipokines, adiponectin expression is a protective cytokine for vascular health and lowered concentrations have been demonstrated in visceral obesity, insulin resistance, diabetes mellitus, metabolic syndrome and hypertension independent of body mass index (Mathieu et al, 2009; Zeugmann et al, 2010; Taylor et al, 2010; Yadav et al, 2012;

Baden et al, 2012; Matsuzamwa et al, 2011). Adiponectin has also been linked to mood regulation (Wilhelm et al, 2012), but results are contradictionary.

The primary objective of the present study was to explore the association between depressive symptom clusters and the metabolic syndrome as well as its individual components in a community-based sample of middle-aged and older persons. We hypothesised that we would find an association between especially the somatic-affective symptom cluster of depression with the metabolic syndrome and/or its individual components. Our second objective was to explore the role of adiponectin within these associations, hypothesising mediating effects of adiponectin within the associations found.

Methods

Sample

The present sample was drawn from the Nijmegen Biomedical Study (NBS), a population-based survey conducted in the Eastern part of The Netherlands among people aged 20 through 90 years. For details we refer to a previous publication (Hoogendoorn et al, 2006). In 2004 and 2005 a questionnaire was sent to all participants (n=2807) in the age group 50 through 70 years. This questionnaire contained items on general health, use of medication and psychiatric symptoms (including the Beck Depression Inventory). A total of 2114 persons were invited to participate in a study on atherosclerosis, of which 1517 (72%) persons responded positively. These participants were invited to come to the hospital in order to participate in a detailed assessment of atherosclerotic disease, its risk factors and consequences (see Holewijn et al, 2010). This latter group was considered eligible for the present study. The Medical Ethics Committee of the Radboud University Medical Centre Nijmegen approved the study protocol (in accordance with the Declaration of Helsinki), and all participants provided written informed consent.

Variables of interest

Depressive symptoms - Depressive symptoms were measured with the Beck Depression Inventory (BDI-I). The BDI-I is a 21-item self-report questionnaire with excellent psychometric characteristics (Beck et al, 1987). Each item is rated on a 0 to 3 scale, with 0 representing 'absence' and 1-3 representing increasing levels of severity of the symptom. The BDI-I yields a total score ranging from 0 to 63. Based on previous research in this field, a sum score ≥10 is indicative of clinically significant depressive symptoms (Marijnissen et al, 2011).

Metabolic syndrome - The Metabolic syndrome (MS) was defined according to the International Diabetes Federation (IDF) (www.idf.org/webdata/docs/IDF-Meta_def_final.pdf, 2006). Taking into account the use of antihypertensives and anti-diabetics the following individual components of the MS were measured. Systolic blood pressure and diastolic blood pressure were measured using an oscillometricsphygmanometer (Criticon model no. 1846, Criticon Inc., USA). Waist circumference was measured at the level of the umbilicus. Triglycerides, HDL cholesterol and glucose concentrations were determined using commercially available enzymatic reagents (AEROSET1 System, Abbott, USA).

Adiponectin - Plasma concentration of Adiponectin was determined using enzyme-linked immune sorbent assays (Elisadevelopment System, Duoset, R&D Systems, Minneapolis, MN, USA). All lipid-lowering medication, when used, was discontinued for 4 weeks prior to the measurements (Holewijn et al, 2010).

Covariates

In addition to age and sex, the following potential confounders were a priori considered in our analyses based on their relationship with depressive symptoms and obesity. The first set of confounders included lifestyle factors such as smoking, use of alcohol, physical activity and use of psychotropic drugs known to affect body weight (Simon et al, 2008). Smoking was based on self-reported information and classified as current, former or never. Use of alcohol was based on the number of standardized units per week. Excessive use (>21 drinks/week for men, >14 drinks/week for women) was assessed. Physical activity was based on the number of exercise sessions per week of more than 30 minutes of moderate to vigorous activity (Stampfer et al, 2000) and dichotomized as 0 or 1 session versus 2 or more sessions. The use of psychotropic drugs was based on self-report data regarding the previous month. People were instructed to collect medication containers before filling in this questionnaire. The use of antidepressants, lithium and antipsychotic drugs as psychotropic drugs were included as these drugs influence body weight (Schwartz et al, 2004). Somatic co-morbidity, other than cardiovascular disease or diabetes mellitus was lumped together and coded as present or absent.

Statistical Methods

Missing items on the BDI were imputed with the series mean in case 1 or 2 items were missing. As the BDI sum score had a skewed distribution in our sample, we applied a log-transformation in order to obtain a normal distribution. All further analyses were conducted using the log-transformed sum score. All other variables were normally distributed.

Principal components analysis (PCA) was conducted on the 21 individual BDI items to

obtain fewer factors/components while retaining the original item information (Marijnissen et al, 2011). PCA was selected as factor extraction method for two reasons: its ultimate goal is to reduce data into components useful for other purposes, and it has superior ability to remedy multicolinearity between factors should it exist (Costello et al, 2009). Varimax rotation was selected because it forces factors to be uncorrelated. Factor scores were calculated on the basis of unstandardized item factor loadings and transformed into standardized z scores (using the Anderson-Rubin method) to increase their interpretability. The scree plot of eigenvalues and the number of complex items revealed a two-factor solution as the optimal solution, comparable with the traditional two-factor structure of the BDI (cognitive-affective versus somatic-affective symptoms), as in a previous factor analysis of the BDI in a Dutch cardiac population (de Jonge et al, 2006). In our sample, the explained variance is 24.1% for factor 1 (cognitive-affective symptoms) and 7.6% for factor 2 (somatic-affective symptoms) (Kaiser-Meyer-Olkin measure of sampling adequacy = 0.898, Bartlett test of sphericity chi-square = 5.074, degrees of freedom (df) = 210, P< .001) (See Marijnissen et al, 2011). See chapter 3 in *Statistical methods* for description of the principal components analysis and chapter 3 *Table 1* for the factor loadings of the depressive symptom dimensions.

The metabolic syndrome (yes/no), the number of metabolic risk factors (range 0 – 5) and the individual components of the metabolic syndrome were regressed separately on the BDI sum score as well as the BDI symptom cluster indices (i.e. the standardized factor scores on the cognitive affective cluster and somatic affective clusters) by multiple linear regression models. All analyses were fully adjusted for the potential confounders described above.

Subsequently, we examined the association between adiponectin and depression using multiple linear regression models with BDI sum score as well as the somatic-affective and cognitive-affective cluster indices as the dependent variables. These models were also fully adjusted for the confounders described above. In case of a significant association, we added adiponectin to the final model to examine a potentially mediating role of adiponectin. A change of 10% of B between the depression measure and metabolic component was considered a relevant degree of mediation. Furthermore, effect-modification was checked by subsequently including interaction terms between adiponectin and the MS as well as its individual components in the different models.

Analyses were carried out using the Statistical Package for the Social Sciences (SPSS) version 17.0 (Inc. Chicago).

Results

Of the 1517 subjects who had consented to participate in the study of non-invasive measurements of atherosclerosis, 240 participants were excluded. Reasons for exclusion were not responding to the postal questionnaire containing the BDI (n=185); having 3 or more missing items on the BDI (n=37); missing data for any of the metabolic syndrome components (n=7), or violating the rules for a reliable measurement of atherosclerotic disease or its risk factors (i.e. having smoked before coming to the hospital, n=4; not obeying the fasting rule, n=2; and not stopping their lipid lowering medication, n=5). This left a final study sample of 1277 people of which all characteristics are described in Table1.

Excluded subjects (240/1517, 15.8%) differed from included subjects (n=1277) with respect to age (62.1 (SD=5.9) versus 61.1 (SD=5.9) years; t=2.54, df=1515, p=.011), current smoking (26.5% versus 17.0%; χ^2=12.0, df=1, p=.001), excessive alcohol usage (7.1% versus 11.7%; χ^2=4.3, df=1, p=.037), somatic co-morbidity other than cardio-vascular disease or diabetes mellitus (6.7% versus 14.4%, χ^2=10.3, df=1, p=.001). No differences were found with respect to any of the metabolic parameters.

We found that the metabolic syndrome was associated with depressive symptoms in our whole sample (see Table 2). This association was stronger when we included the total number of risk factors as a independent variable than when simply using the presence or absence of the metabolic syndrome (B=0.030, β=.11, p<.001 and B=0.047, β= .06, p=.022, respectively). Examining the cognitive-affective symptom cluster and the somatic-affective symptom cluster, separately, we found that the metabolic syndrome was specifically associated with somatic-affective symptoms (B=0.196, β=.09, p=.001). Also waist circumference, triglycerides, HDL cholesterol and diabetes or increased glucose were specifically associated with the somatic-affective symptoms in separate regression analyses (B=0.011, β=.14, p<.001; B=0.086, β=.07, p=.010; B=-0.252, β=-.09, p=.002, B=0.077, β=.05, p=.051, respectively). In contrast, diastolic blood pressure was specifically associated with the cognitive-affective symptom cluster (B =-0.006, β=-.060, p=.038). Overall, associations were stronger in males compared to females.
With respect to sex differences, we found that waist circumference was associated with depressive symptoms in both sexes (males: B=0.003, β=.10, p=.013; for females: B=0.004, β=.13, p=.001), whereas triglycerides and HDL cholesterol were associated with depressive symptoms only in males (B=0.029, β=.08, p =.050 and B=-0.156, β=-0.14 p<.001, respectively).

Table 1. Characteristics of study population (n=1277).

Characteristic	Whole sample (n=1277)	Males (n=627)	Females (n=650)	Statistics
Demographic				
• Age, mean (SD)	61.1 (5.9)	61.7 (5.9)	60.4 (5.8)	t=4.1, df=1275, p<.001
• Male, n (%)	627 (49.1)	-	-	-
• Chronic somatic disease, n (%)[b]	184 (14.4)	82 (13.1)	102 (15.7)	χ^2=1.8, df=1, p=.184
Beck Depression Inventory sum score				
• Median (IQR)	4 (2 – 8)	4 (1 – 6)	5 (3– 9)	t=-5.8, df=1275, p<.001[a]
• ≥10, n (%)	213 (16.7)	81 (12.9)	132 (20.3)	χ^2=12.5 df=1, p<.001
Lifestyle factors, n (%)				
• Current smoking	217 (17.0)	101 (16.1)	116 (17.9)	χ^2=0.7, df=1, p=.394
• Excessive alcohol usage[c]	150 (11.8)	71 (11.3)	79 (12.2)	χ^2=0.2, df=1, p=.645
• Sports ≥2 times a week	466 (36.5)	231 (36.8)	235 (36.2)	χ^2=0.1, df=1, p=.798
• Use of psychotropic drugs	51 (4.0)	12 (1.9)	39 (6.0)	χ^2=13.9, df=1, p<.001
Metabolic Syndrome (MS), n (%)	425 (33.3)	235 (37.5)	190 (29.2)	χ^2=9.8, df=1, p=.002
No of risk factors MS, mean (SD)	2.1 (1.3)	2.2 (1.3)	2.0 (1.3)	t=2.6, df=1275, p<.001
• Waistcircumference, mean (SD)	94.3 (12.4)	99.6 (10.6)	89.2 (11.7)	t=16.6, df=1275, p=.008
• DM or increased glucose, n (%)	78 (6.1)	49 (7.8)	29 (4.5)	χ^2=6.3, df=1, p=.012
• Systolic blood pressure, mean (SD)	129 (15)	130 (14)	127 (16)	t=4.3, df=1275, p<.001
• Diastolic blood pressure, mean (SD)	78 (10)	81 (9)	75 (11)	t=10.1, df=1275, p<.001
• Total cholesterol, mean (SD)	5.9 (1.0)	5.7 (1.0)	6.0 (1.0)	t=-5.7, df=1275, p<.001
• High-density cholesterol, mean (SD)	1.4 (0.4)	1.3 (0.3)	1.5 (0.4)	t=-14.3, df=1275, p<.001
• Triglycerides, mean (SD)	1.4 (0.8)	1.6 (0.4)	1.3 (0.6)	t=5.4, df=1275, p<.001
• Adiponectin, median (IQR)	4.2 (2.2)	3.2 (1.5)	5.2 (2.3)	t=-18.1, df=1275, p<.001

[a] Differences tested by t-test on the log-transformed BDI sumscore
[b] Chronic somatic disease (yes/no) point to current treatment for any somatic disease other than cardio vascular disease or diabetes mellitus; counted were diseases of the lung, kidney, liver, colon, immune system or having had a history of cancer.
[c] Excessive alcoholusage: > 21drinks/week for men, > 14drinks/week for women

Irrespective of sex, all associations found between depression and metabolic syndrome or its components were mainly driven by the somatic-affective symptom cluster (see also Table 2).

Adiponectin showed neither a linear nor a U-shape association with depressive symptoms or symptom profiles in the whole sample as well as when stratified for sex

Table 2 Association between metabolic syndrome (components) and depressive symptoms[a].

	BDI sum score			BDI symptom dimension[b]					
				Cognitive-affective cluster			Somatic-affective cluster		
Sample	B	β	*P* value	B	β	*P* value	B	β	*P* value
Whole sample (n=1277)									
Metabolic Syndrome (yes/no)	0.047	.063	.022	-0.004	.875	.515	0.196	.092	.001
Metabolic Syndrome (no. of risk factors)	0.030	.112	<.001	0.008	.010	.717	0.100	.128	<.001
• Waist circumference	0.003	.120	<.001	0.003	.043	.165	0.011	.135	<.001
• Triglycerides (mmol/l)	0.028	.066	.016	0.005	.004	.879	0.086	.070	.010
• HDL cholesterol (mmol/l)	-0.087	-.091	.002	-0.113	-.042	.173	-0.252	-.093	.002
• Systolic blood pressure	0.000	-.013	.633	-0.003	-.042	.147	0.002	.025	.366
• Diastolic blood pressure	-0.002	-.046	.102	-0.006	-.060	.038	-0.001	-.009	.757
• Diabetes (or increased Glucose)	0.077	.053	.051	-0.020	-.005	.865	0.319	.076	.005
Males (n=627)									
Metabolic Syndrome (yes/no)	0.047	.064	.110	-0.026	-.014	.732	0.175	.088	.026
Metabolic Syndrome (no. of risk factors)	0.032	.119	.003	0.002	.003	.938	0.100	.135	.001
• Waist circumference	0.003	.099	.013	0.001	.017	.682	0.011	.116	.003
• Triglycerides (mmol/l)	0.029	.077	.050	0.004	.004	.920	0.085	.083	.033
• HDL cholesterol (mmol/l)	-0.156	-.139	<.001	-0.152	-.051	.214	-0.473	-.146	<.001
• Systolic blood pressure	-0.001	-.035	.394	-0.005	-.074	.075	0.001	.008	.838
• Diastolic blood pressure	-0.001	-.030	.448	-0.007	-.071	.077	0.002	.016	.685
• Diabetes or increased glucose	0.094	.071	.074	-0.048	-.015	.719	0.351	.098	.012
Females (n=650)									
Metabolic Syndrome (yes/no)	0.046	.063	.107	0.010	.004	.912	0.221	.099	.010
Metabolic Syndrome (no. of risk factors)	0.028	.107	.006	0.016	.019	.636	0.099	.124	.001
• Waist circumference	0.004	.127	.001	0.005	.055	.156	0.011	.132	.001
• Triglycerides (mmol/l)	0.029	.056	.149	0.022	.013	.742	0.092	.058	.130
• HDL cholesterol (mmol/l)	-0.044	-.051	.197	-0.099	-.034	.385	-0.129	-.048	.211
• Systolic blood pressure	0.000	.005	.895	-0.001	-.015	.702	0.003	.040	.314
• Diastolic blood pressure	-0.002	-.060	.121	-0.005	-.049	.210	-0.003	-.027	.480
• Diabetes or increase glucose	0.046	.029	.457	0.019	.003	.928	0.264	.054	.156

[a] Linear regression analyses adjusted for age, sex, smoking (yes/no), severe alcohol (yes/no), sports (0 -1 vs >=2), use of weight gaining psychotropic drugs (yes/no), chronic co-morbidity (yes/no)
[b] Symptom profiles based on PCA with varimax rotation.

(all p-values >.16). (See Table 3). Adiponectin thus by definition could not mediate the association between depression and metabolic health indices. Subsequently, we explored whether adiponectin moderated the effect of metabolic health indices on the total BDI sum score, cognitive-affective symptom cluster and somatic affective symptom cluster in the whole sample or in a sex-specific way. None of the 72 interaction terms tested were significant at the 5% levels.

Table 3 Association between adiponectin and depressive symptoms.

	BDI sum score			BDI symptom dimension					
				Cognitive affective cluster			Somatic affective cluster		
Association with adiponectin[a]	B	*β*	*P* value	B	*β*	*P* value	B	*β*	*P* value
• Whole sample (n=1277)	0.001	.004	.890	0.023	.052	.094	-0.019	-.042	.161
• Males (n=627)	-0.004	-.018	.655	0.005	.008	.837	-0.033	-.053	.170
• Females (n=650)	0.003	.020	.606	0.034	.072	.067	-0.014	-.032	.407

[a] Linear regression analyses adjusted for age, sex, smoking (yes/no), severe alcohol (yes/no), sports (0 -1 vs >=2), use of weight gaining psychotropic drugs (yes/no), chronic co-morbidity (yes/no)

Discussion

Main findings

We show that the association between the metabolic syndrome and depressive symptoms is primarily driven by the somatic-affective symptom cluster of depression. In both sexes, the number of risk factors of the metabolic syndrome shows a stronger association with depressive symptoms than simply the presence of the metabolic syndrome. In women, however, the waist circumference is the sole factor driving the association, whereas in men the association is driven by waist circumference, HDL cholesterol and triglycerides. In contrast to our expectations, adiponectin neither mediated nor moderated these associations.

Relation between metabolic syndrome and depressive symptoms

The association between the metabolic syndrome and depression is in line with the hypothesis of 'metabolic depression', a subtype of depression with a chronic course.

Waist circumference seems the most important metabolic syndrome feature in relation to depression (Vogelzangs et al, 2011). Interestingly, the predictive value of obesity for the onset of depression may be dependent on metabolic health as only metabolically unhealthy obese compared to metabolically healthy obese persons had an elevated risk of developing depressive symptoms (Hamer et al, 2012). We extend these findings by pointing to sex-specificity of findings and depressive symptom profiles.

Firstly, the sex differences in our study are intriguing. Although the strength of the overall association between number of metabolic risk factors was similar in males (β =0.12) and females (β =0.11), in males several individual components were associated with depressive symptoms, whereas in females the association was confined to waist circumference only. Two explanations could be put forward. First, as results for the individual components are less pronounced in women, but all are in the same direction, it could also be explained by the fact that vascular disease in females develops at a later age (Roger et al, 2012; Van de Leeuw et al, 2013) as well as the relative importance of other pathways to depression in women, like neuroticism (Sutin et al, 2010). Secondly, it may point to pathophysiological differences between male and female depression. Parallel to our sex-specific findings for HDL-cholesterol levels, previous studies on the association between cholesterol levels and depression also demonstrated sex-specific effects (Tedders et al, 2011; Ancelin et al, 2010).

Secondly, the association between depressive symptoms and metabolic syndrome or its components relies primarily on the somatic-affective symptom cluster. Somatic-affective symptoms of depression largely overlap with features of sickness behaviour, including general weakness and fatigue, which are generally thought to be induced by inflammatory processes (Dantzer et al, 2008). Interestingly, a recent study found inflammation specifically associated with somatic-affective symptoms (Duivis et al, 2013). This is in line with studies in which somatic-affective, but not cognitive-affective symptoms of depression predict cardiovascular morbidity and mortality (de Jonge et al, 2006; Linke et al, 2009). Together, these findings may point to a specific subtype of depression.

Relation between depressive symptoms and adiponectin, as a mediating factor

In contrast to our expectations, adiponectin neither mediated nor moderated the associations between depression and metabolic health. Our results are in contrast with recent finding that depressed inpatients with the metabolic syndrome (n=17) had a lower adiponectin level then patients without the metabolic syndrome (n=53) (Zeugmann et al, 2010) suggesting an additive affect of the metabolic syndrome and

major depression on adiponectin levels. Nonetheless, studies on adiponectin in depression have reported inconsistent results. Two studies have reported negative findings: one study did not find any association between depressive symptoms and adiponectin level (Pan et al, 2008), the other study did not find any difference in adiponectin levels in depressed individuals before and after treatment with antidepressive medication (Chen et al, 2010). In contrast, several other studies did find decreased plasma adiponectin level in patients with a major depression (Cizza et al, 2010; Lehto et al, 2010; Diniz et al, 2012), although one study also found an inverse effect of elevated adiponectin levels in elderly with subsyndromal depression (Jeong et al, 2012). These inconsistencies suggest a complex relation between depression and adiponectin. As adiponectin has been extensively linked to cardiovascular and inflammatory pathways (Lago et al, 2007; Mathieu et al, 2009; Taylor et al, 2010; Fernandez-Sanchez et al, 2011; Hui et al, 2012), we also examined interactions between the different metabolic health parameters and adiponectin on the association with depression. The results of these exploratory analyses, however, were rather negative.

Methodological considerations

Some limitations of this study have to be acknowledged for proper interpretation. First, the cross-sectional design limits causal interpretation of the findings. Second, being a population-based survey, some selection bias might have occurred toward the healthier part of the population. Finally, we did not measure depression according to formal diagnostic criteria. Although depressive symptoms are generally considered on a continuum with depressive disorder, it is not clear whether this assumption holds true. Especially lower levels of depressive symptoms in the population may be confounded by underlying somatic illnesses (Thoms et al, 2010). This limitation might also explain the negative findings with respect to adiponectin.

Final conclusion and clinical implications

Although the pathophysiological mechanisms underlying the association between metabolic disturbances and depression remains to be elucidated, our study point to sex-differences as well as a specific phenotype of depression that is associated with metabolic disturbances. Future studies on the concept of metabolic depression should therefore take different symptom dimensions of depression into account.

References

Akbaraly TN, Ancelin ML, Jaussent I et al. (2011) Metabolic syndrome and onset of depressive symptoms in the elderly. *Diabetes Care;* 34 (4):904-909.

Ancelin ML, Carriere I, Boulenger JP et al. (2010) Gender and genotype modulation of the association between lipid levels and depressive symptomatology in community-dwelling elderly (the ESPRIT study). *Biol Psychiatry;* 68 (2):125-132.

Baden MY, Yamada Y, Takahi Y et al. (2012) Association of adiponectin with blood pressure in healthy people. *Clin Endocrinol.* doi: 10.1111/j.1365-2265.2012.04370.x. [Epub ahead of print].

Beck AT, Steer RA. (1987) Manual for the Revised Beck Depression Inventory 1. San Antonio, Tex, Psychological corporation.

Beekman ATF, Copeland JRM, Prince MJ et al. (1999) Review of community prevalence of depression in later life. *Br J Psychiatry;* 174:307-311.

Bus BA., Marijnissen RM, Holewijn S et al. (2011) Depressive symptom clusters are differentially associated with atherosclerotic disease. *Psychol Med;* 41(7):1419-1428.

Chen Y, Lin W, Chen Y et al. (2010) Antidepressant effects of Insulin sensitivity and proinflammatory cytokines in the depressed males. *Mediators of inflammation;* 1-7.

Cizza G, Nguyen VT, Eskandari F et al (2010) Low 24-hour Adiponectin and high nocturnal leptin concentrations in a case-control study of community-dwelling premenopausal women with major depressive disorder: the Premenopausal, Osteopenia/Osteoporosis, Women, Alendronate, Depression (POWER) study. *J Clin Psychiatry;* 71(8):1079-87

Costello A, Osborne J. (2009) Best practices in exploratory factor analysis: four recommendations for getting the most from your analysis. Practical Assessment Research and Evaluation. 10. Available online: http://pareonline.net/getvn.asp?v=10&n=7

Dantzer R, O'Connor JC, Freund GG et al. (2008) From inflammation to sickness and depression: when the immune system subjugates the brain. *Nat Rev Neurosci;* 9(1):46-56.

De Jonge P, Ormel J, van den Brink RH et al. (2006) Symptom dimensions of depression following myocardial infarction and their relationship with somatic health status and cardiovascular prognosis. *Am J Psychiatry;* 163(1):138-144.

Diniz BS, Teixeira AL, Campos AC et al. (2012) Reduced serum levels of adiponectin in elderly patients with major depression. *J Psychiatr Res;* 46(8):1081-5.

Fernandez-Sanchez A, Madrigal-Santillan E. Bautista M et al. (2011) Inflammation, Oxidative Stress and Obesity. *Int J Mol Sci;* 12:3117-3132.

Gale CR. Kivimaki M. Lawlor DA et al. (2010) Fasting Glucose, Diagnosis of Type 2 Diabetes and Depression: the Vietnam Experience Study. *Biol Psychiatry;* 67:189-192.

Hamer M, Batty GC, Kivimaki M. (2012) Risk of future depression in people who are obese but metabolically healthy: the English longitudinal study of ageing. *Mol Psychiatry;* 17(9):940-5.

Holewijn S, den Heijer M, van Tits LJ et al. (2010) Impact of waist circumference versus adiponectin level on subclinical atherosclerosis: a cross-sectional analysis in a sample from the general

population. *J Intern Med;* 267(6):588-98.

Hoogendoorn EH, Hermus AR, de Vegt F et al. (2006) Thyroid function and prevalence of anti-thyroperoxidase antibodies in a population with borderline sufficient iodine intake: influences of age and sex. *Clin Chem;* 52(1):104-11.

Howren MB, Lamkin DM, Suls J. (2009) Associations of depression with C-Reactive Protein, IL-1, and IL-6: A Meta-Analysis. *Psychosomatic medicine;* 71:171-186.

Hui X, Lam KS, Vanhoutte PM et al. (2012) Adiponectin and cardiovascular health: an update *Br J Pharmacol;* 165(3):574-90.

Jeong HC, Jun Min B, Lim S et al. (2012) Plasma Adiponectin elevation in elderly individuals with subsyndromal depression. *Psychoneuroendocinology;* 37:948-955.

Koponen H, Jokelainen J, Keinanen-Kiukaanniemi S et al. (2008) Metabolic syndrome predisposes to depressive symptoms: a population-based 7-year follow-up study. *J Clin Psychiatry;* 69(2):178-82.

Lago F, Dieguez C, Gomez-Reino J et al. (2007) Adipokines as emerging mediators of immune response and inflammation. *Nat Clin Pract Rheumatol;* 3(12):716-24.

Lamers F, Vogelzangs N, Merikangas KL et al. (2012) Evidence for a differential role of HPA-axis function, inflammation and metabolic syndrome in melancholic versus atypical depression. *Mol Psychiatry;* Oct 23. doi: 10.1038/mp.2012.144. [Epub ahead of print]

Lehto SM, Huotari A, Niskanen L et al. (2010) Serum adiponectin and resistin levels in major depressive disorder. *Acta Psychiatr Scand;* 121(2):209-15.

Linke SE, Rutledge T, Johanson BD et al. (2009) Depressive symptoms dimensions and cardiovascular prognosis among women with suspected myocardial ischemia: a report from the National Heart, Lung, and Blood Institute-sponsored Women's Ischemia Syndrome Evaluation. *Archives of General Psychiatry;* 66:499-507.

Luppino FS, de Wit LM, Bouvy PF et al. (2010) Overweight, obesity and depression: a systematic review and meta-analysis of longitudinal studies. *Arch Gen Psychiatry;* 67(3):220-9.

Marijnissen RM, Bus BA, Holewijn S et al. (2011) Depressive symptom clusters are differentially associated with general and visceral obesity. *J Am Geriatr Soc;* 59(1):67-72.

Mathieu P, Poirier P, Pibarot P et al. (2009) Visceral Obesity: the link among inflammation, hypertension and cardiovascular disease. *Hypertension;* 53:577-584.

Matsuzamwa Y, Funahashi T, Nakamura T. (2011) The concept of metabolic syndrome; contribution of visceral fat accumulation and its molecular mechanism. *J Atheroscler Thromb;* 18:629-639.

Milaneschi Y, Simonsick EM, Vogelzangs N et al. (2012) Leptin, abdominal obesity and onset of depression in older men and women. *J Clin Psychiatry;* 73(0):1205-11.

Pan A, Ye X, Franco OH et al. (2008). The association of depressive symptoms with inflammatory factors and adipokines in middle-aged and older Chinese. *Plos One*; 3(1): e1392.

Pan A, Keum N, Okereke O et al. (2012) Bidirectional association between depression and metabolic syndrome. *Diabetes;* 35:1171-1180.

Roest AM, Thombs BD, Grace SL et al (2011) Somatic/affective symptoms, but not cognitive/affective symptoms, of depression after acute coronary syndrome are associated with 12-month all-cause mortality. *J Affect Disord;* 131(1-2):158-63.

Roger VL, Go AS, Lloyd-Jones DM et al. (2012) Heart disease and stroke statistics-2012 update: a report from the American heart Association. *Circulation;* 24:e2-e220.

Schwartz TL, Nihalani N, Virk S et al. (2004) Psychiatric medication-induced obesity: treatment options *Obesity Reviews;* 5(4):233-238.

Simon GE, Ludman EJ, Linde JA et al. (2008) Association between obesity and depression in middle-aged women. *Gen Hosp Psychiatry;* 30(1): 32-39.

Stampfer MJ, Hu FB, Manson JE et al. (2000) Primary prevention of coronary heart disease in women through diet and lifestyle. *N Engl J Med;* 343:16-22.

Sutin AR, Beason-Held LL, Dotson VM et al. (2010) The neural correlates of neuroticism differ by sex prospectively mediate depressive symptoms among older women. *J Affect Disord;* 127:241-247.

Taylor VH, Macqueen G. (2010). The role of adipokines in understanding the associations between obesity and depression. *J Obes;* pil 748048. Doi: 10.1155/2010/748048. Epub 2010 Jul 28.

Tedders SH, FoKong KD, McKenzie LE et al. (2011) Low cholesterol is associated with depression among US household population. *J Affect Disord;* 135:115-121.

Thoms BD, Ziegelstein RC, Pilote L et al. (2010) Somatic symptom overlap in Beck Depression Inventory-II scores following myocardial infarcation. *Br J Psychiatry*; 197:61-66.

Van der Leeuw J, Wassink AMJ, van der Graaf Y et al. (2013) Age-related difference in abdominal fat distribution in premenopausal and postmenopausal women with cardiovascular disease. *Menopause;* 20(4) DOI: 10.1097/gme.0b013e31827212a5.

Vogelzangs N, Kritchevsky SB, Beekman AT et al. (2008) Depressive symptoms and change in abdominal obesity in older persons. *Arch gen psychiatry;* 65 (12):1386-1393.

Vogelzangs N, Beekman AT, Boelhouwer IG et al. (2011) Metabolic depression: a chronic depressive subtype? Findings from the InCHIANTI study of older persons. *J Clin Psychiatry;* 72(5):598-604.

Wilhelm CJ, Choi D, Huckans M et al. (2012) Adipocytokine signaling is altered in flinders sensitive line rats, and adiponectin correlates in humans with some symptoms of depression. *Pharmacol Biochem Behav;* 103(3):643-651.

Yadav A, Kataria MA, Saini V et al. (2012) Role of leptin and adiponectin in insulin resistance. *Clin Chim Acta;* pii: S0009-8981(12)00577-3. doi: 10.1016/j.cca.2012.12.007. [Epub ahead of print].

Zeugmann S, Quante A, Heuser I et al. (2010) Inflammatory biomarkers in 70 depressed inpatients with and without the metabolic syndrome. *J Clin Psychiatry;* 71(8):1007-16.

Depressive symptom profiles are differentially associated with general and visceral obesity

Published

Depressive symptom clusters are differentially associated with general and visceral obesity

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Abstract

Background – Depressive symptoms and obesity, both risk factors for unfavourable health outcomes, are mutually related although mixed results have been reported. We examined the relationship between obesity and depressive symptoms taking into account different measures for obesity, i.e. Body Mass Index (BMI), Waist circumference (WC) and Waist-to-Hip Ratio (WHR), as well as different depressive symptom clusters.
Methods – Cross-sectional population-based survey. Baseline data of the Nijmegen Biomedical Study. Participants: 1284 persons aged 50 through 70 years. Obesity (BMI, WC and WHR) and depressive symptoms were measured, the latter using the Beck Depression Inventory (BDI). Principal components analysis of the BDI-items yielded two factors, representing a cognitive-affective symptom cluster and a somatic-affective symptom cluster. Multiple regression analyses corrected for confounders were conducted for each measure of obesity, with separate models testing the BDI sum score and both depression symptom clusters, respectively.
Results – The BMI was significantly associated with both the BDI sum score (β=.12, p<.001) as well as cognitive and somatic-affective symptom clusters (β=.08, p=.008 and β=.10, p=.001, respectively). The WC and WHR, however, were specifically associated with the somatic-affective symptom cluster (β=.11, p<.001 and β=.07, p=.004, respectively).
Conclusions – Visceral obesity, which is more indicative of vascular risk than BMI, is specifically associated with somatic-affective depressive symptom cluster, which might suggest that these symptoms are primarily due to a (subclinical) somatic condition.

Keywords

Depression, Obesity, Aged, Body Mass Index (BMI), Waist Circumference (WC)

Introduction

Depression and obesity are risk factors for unfavourable health outcomes, especially cardiovascular disease (CVD) (Faith et al, 2002; Barry et al, 2008; Allison et al, 2009; Everson-Rose et al, 2009). The prevalence of clinically relevant depressive symptoms is estimated at 13.5% of elderly people in the community (Beekman et al, 1999). According to the World Health Organization during the past 20 years, the prevalence of obesity (body mass index (BMI) ≥ 30 kg/m2) in all age groups has more than doubled in Western countries, leading to a prevalence rate of more than 20% in the United States and over 15% in European countries. Most studies report a positive association between obesity and more-severe depressive symptoms (Stunkard et al, 2003; Sachs-Ericsson et al, 2007; De Wit et al, 2009; Luppino et al, 2010), although an absent or even an inverse relationship has also been reported (Carpenter et al, 2000; Ho et al, 2008). Longitudinal studies suggest that depression predicts the onset of obesity and vice versa (Sachs-Ericsson et al, 2007; De Wit et al, 2009; Luppino et al, 2010). Current hypotheses about the predisposition of depressive people to obesity include lifestyle factors and direct effects of psychotropic drugs (Stunkard et al, 2003; Schwartz et al, 2004). Factors that are hypothesized to predispose to depression in the obese include stigma, a negative body image and disappointment about failing diets, as well as activity limitations (Dixon et al, 2003).

In the present chapter, two important limitations of previous studies will be examined more in depth: different measures of obesity and the subtyping of depressive symptoms. In most studies obesity is defined based on the BMI. With increasing age, BMI is less accurate because it does not account for changes in body composition and loss of height, which may lead to an underestimation or overestimation of fatness (Villareal et al, 2005). This is especially relevant because increases in visceral adipose tissue primarily determine the risk of obesity leading to cardiovascular disease (Nicklas et al, 2004). The most convenient anthropometric indices of visceral adipose tissue are the waist-to-hip ratio (WHR) and waist circumference (WC).
Another issue is the subtyping of depression. In patients with depression and CVD, the somatic-affective symptom cluster of depression, but not the cognitive-affective symptom cluster, was related to subsequent vascular events (de Jonge et al, 2006). Similarly, one may hypothesise, that the somatic-affective symptoms of depression are more strongly related to the WHR and WC than the cognitive-affective symptoms.

The objective of the present study was to explore the relationship between depressive

symptoms and obesity in a community-based sample aged 50 through 70 years, taking into account different measures of obesity (BMI, WHR, and WC) as well as the different symptom clusters within the concept of depression. It was hypothesized first that depressive symptoms in later life are associated with obesity and second that visceral measures of obesity are more strongly related to somatic-affective depressive symptoms than to cognitive-affective depressive symptoms.

Methods

Sample

The present sample was drawn from the Nijmegen Biomedical Study (NBS), a population-based survey conducted in the eastern part of The Netherlands of people aged 20 through 90 years (Hoogendoorn et al, 2006). In 2004 and 2005, a questionnaire was sent to all participants (n=2807) aged 50 to 70; 1517 (54%) of these gave additional informed consent to participate in a study on atherosclerosis. These participants visited the hospital for a detailed assessment of atherosclerotic disease, its risk factors and consequences (Holewijn et al, 2010). This latter group was considered eligible for the present study. The Medical Ethics Committee of the Radboud University Nijmegen Medical Centre approved the study protocol.

Variables of interest

Obesity - A trained staff member measured obesity according to a predefined protocol. Weight and height were measured and Body Mass Index (BMI) was calculated as body weight (kg) divided by the square of height (m^2). Waist circumference was measured at the level of the umbilicus, hip circumference was measured at the level of the greater trochanter and WHR was calculated.

Depressive symptoms - Depressive symptoms were measured using the Beck Depression Inventory I (BDI-I). The BDI-I is a 21-item self-report questionnaire with excellent psychometric characteristics (Beck et al, 1987). Each item is rated on a 0 to 3 scale, with 0 representing 'absence' and 1-3 representing increasing levels of severity of the symptom. The BDI-I yields a total score ranging from 0 to 63. Based on previous research in this area, a sum score of 10 or greater is indicative of clinically significant depressive symptoms (Pizzi et al, 2008).

Covariates

In addition to age and sex, the following potential confounders were a priori considered

based on their relationship with depressive symptoms and obesity.
The first set of confounders included lifestyle factors such as smoking, the use of alcohol, physical activity and use of psychotropic drugs known to affect body weight (Simon et al, 2008). Smoking was based on self-reported information and defined as current smoking (yes/no) and formerly smoking (yes/no). Use of alcohol was based on the number of standardized units per week. Excessive use (> 21 drinks/week for men, >14 drinks/ week for women) was corrected for. Physical activity was based on the number of exercise sessions per week of more than 30 minutes moderate to vigorous activity (Stampfer et al, 2000) and dichotomized as 0 or 1 moment versus 2 more sessions. The use of psychotropic drugs was based on self-report data regarding the previous month. People were instructed to collect medication containers first before filling in this questionnaire. We considered the use of antidepressants, lithium and antipsychotic drugs as psychotropic drugs influencing body weight (Schwartz et al, 2004).
The second set of confounders included somatic co-morbidity. Based on its relationship with obesity, diabetes mellitus and cardiovascular disease were evaluated separately. Diabetes mellitus (DM) was defined as a glucose level of 7.0 mmol/litre or higher after an overnight fast or previously diagnosed and treated DM. Cardiovascular disease (CVD) status was assessed during the research visit at the hospital and defined as a self-reported history of myocardial infarction, transient ischemic attack, stroke, peripheral arterial disease, coronary artery bypass /angioplasty, or treated angina pectoris. Other somatic co-morbidity was lumped together and coded as present/absent.

Statistical methods
Because the BDI sum score had a skewed distribution in the sample, a log-transformation was applied to obtain a normal distribution. All further analyses were conducted using the log-transformed sum score. The BMI, WHR and WC were normally distributed.
Principal components analysis (PCA) was conducted on the 21 individual BDI items to obtain fewer factors or components while retaining the original item information. PCA was selected rather than factor analysis for 2 reasons: (1) its ultimate goal is to reduce data into components useful for other purposes; and (2) its superior ability to remedy multicolinearity between factors, should it exist (Costello et al, 2005). Varimax rotation was selected because it forces factors to be uncorrelated. Factor scores were calculated on the basis of unstandardized item factor loadings and transformed into standardized z scores (using the Anderson-Rubin method) to increase their interpretability.
The scree plot of eigenvalues and the number of complex items revealed a 2-factor solution as the optimal solution, comparable to the traditional 2-factor structure of the BDI (cognitive-affective vs somatic-affective symptoms) as well as a previous factor analyses of the BDI in a Dutch cardiac population (Kaiser-Meyer-Olkin measure of

sampling adequacy = .898; Bartlett's test of sphericity: chi-square = 5074; df= 210; p<.001; explained variance factor 1= 24.1%; factor 2= 7.6%) (Table 1) (Beck et al, 1987; de Jonge et al, 2006).

Because a U-shape relationship between obesity and depressive symptoms can explain some inconsistencies between previous studies (de Wit et al, 2009), whether such a relationship existed in this sample was first checked by comparing the depressive symptom scores for four categories of BMI (underweight (BMI ≤20 kg/m2, normal weight (>20.0-≤25 kg/m2), overweight (>25.0-≤30 kg/m2), and obesity (>30 kg/m2). This resulted in the exclusion of 26 patients with underweight (see Results).
Linear regression analyses were conducted with obesity indices as the dependent variables. For each index of obesity (BMI, WHR, and WC), two different models were evaluated. Depressive symptoms were evaluated in the first model by including the log-transformed sum score of the BDI and in the second model by including the two factor scores yielded by the PCA together. All models were corrected for sex, age, life-style factors and somatic co-morbidity (as described above). Sex differences were explored by post-hoc analyses based on studies showing an association of obesity and depression in women only (Carpenter et al, 2000) or abdominal obesity and depression in men only (Herva et al, 2006).
All analyses were performed in SPSS version 17.0 (SPSS, Inc. Chicago, IL).

Results

Of the 1517 subjects who consented to participation in the study of non-invasive measurements of atherosclerosis, 233 participants were excluded, leaving a final study sample of 1284 people. Reasons for exclusion were not responding to the postal questionnaire containing the BDI (n=185); having 3 or more missing items on the BDI (n=37); violating the rules for a reliable measurement of atherosclerotic disease or its risk factors (having smoked before coming to the hospital, n=4; not obeying the fasting rule, n=2; not stopping their lipid lowering medication, n=5). See Table 2 for the clinical characteristics of this sample.
Included subjects (n=1284) did not differ from excluded subjects and subjects not giving additional informed consent (n=1523) with respect to age and sex, but had significantly less severe depressive symptoms (median BDI sum score 4 (Interquartile range (IQR): 2 – 8) vs 5 (IQR: 2 – 9); Z=-2.4, p=.018).

Table 1 Factor loadings of depressive symptom dimensions and relation to Beck Depression Inventory items and previous dimensional constructs.

Items of the Beck Depression Inventory	Original Beck & Steer dimensional structure	Dimensional structure De Jonge et al (2006)			Dimensional structure[a] present study	
		Cognitive - Affective factor	Somatic - Affective factor	Appetitive factor	Cognitive - Affective factor	Somatic - Affective factor
Sadness	Cognitive	0.45	0.64		0.48	0.35
Pessimism	Cognitive	0.58	0.56		0.58	0.28
Sense of failure	Cognitive	0.66			0.66	0.11
Dissatisfaction	Cognitive	0.49	0.69		0.43	0.52
Guilt	Cognitive	0.70			0.59	0.09
Punishment	Cognitive	0.59			0.49	0.08
Self-dislike	Cognitive	0.72			0.72	0.05
Self-accusations	Cognitive	0.71			0.67	0.08
Suicidal ideas	Cognitive	0.49			0.63	0.08
Crying	Cognitive		0.52		0.31	0.38
Irritability	Cognitive		0.45		0.17	0.43
Social withdrawal	Cognitive	0.51	0.42		0.22	0.38
Indecisiveness	Cognitive	0.40	0.68		0.40	0.46
Body image change	Somatic	0.57			0.37	0.22
Work difficulty	Somatic		0.69		0.23	0.64
Insomnia	Somatic		0.55		0.22	0.44
Fatigability	Somatic		0.58		0.00	0.60
Loss of appetite	Somatic		0.42	0.65	-0.03	0.51
Weight loss	Somatic			0.66	-0.02	0.24
Somatic preoccupation	Somatic		0.67		0.16	0.47
Loss of libido	Somatic		0.50		0.11	0.49

[a] Rotate component. Extraction method: Principal Component Analysis. Rotation method Varimax with Kaiser Normalization.

Table 2 Baseline characteristics of the 1284 included participants.

Demographics		
• Age (years)	Mean (SD)	61 (6)
• Male sex	n (%)	630 (49)
Depression		
• BDI sum score	Median (IQR)	4 (2 - 8)
• BDI sum score >= 10	n (%)	214 (16.7)
Measures of obesity		
• Body Mass Index (kg/m^2)	Mean (SD)	26.7 (4.0)
• Waist circumference (cm)	Mean (SD)	94 (12)
• Waist Hip Ratio	Mean (SD)	0.90 (0.08)
Lifestyle factors		
• Current smoking	n (%)	219 (17)
• Excessive alcohol usage	n (%)	152 (12)
• Sports 2 or more times a week	n (%)	469 (37)
• Use of psychotropic drugs*	n (%)	51 (4)
Somatic co-morbidity		
• Cardiovascular disease	n (%)	151 (12)
• Diabetes Mellitus type 1 or 2	n (%)	78 (6)
• Other chronic diseases	n (%)	184 (14)

* 48 participants used antidepressant drugs (of which 1 also lithium and 2 also an antipsychotic drug), 3 only lithium, and 1 only an antipsychotic drug.

Abbreviations: SD, standard deviation; n, number of participants; BDI, Beck Depression Inventory; IQR, Interquartile Range

First, the existence of a U-shaped relationship between obesity and depressive symptoms was examined by comparing the severity of depressive symptoms within four categories of weight. The analysis of covariance using the log-transformed BDI score and corrected for all potential confounders yielded significant overall effect (F=3.8, df=3, p=.01), showing significantly higher depressive symptoms in the obese category than in the normal weight (LSD post-hoc, p=.001) and overweight category (LSD post-hoc, p=.040), but not the underweight category (LSD post-hoc, p=.96). Similar results were found with respect with the somatic-affective depressive symptom cluster, whereas no significant relationship was found with the cognitive-affective symptom cluster. Given this U-shaped relationship between depression and BMI, and the interest

Table 3 Fully adjusted multivariate regression analyses of depressive symptoms on different measures of obesity[a].

	Obesity		Visceral obesity			
	Body Mass Index		Waist circumference		Waist Hip Ratio	
	β	*P* value	*β*	*P* value	*β*	*P* value
Whole sample (n=1258)						
Model 1						
Continuous BDI score (log10)	.12	<.001	.10	<.001	.04	.068
Model 2						
Cognitive BDI score	.08	.008	.04	.092	-.01	.61
Somatic BDI score	.10	.001	.11	<.001	.07	.004
Men (n=625)						
Model 1						
Continuous BDI score (log10)	.09	.027	.08	.043	.05	.23
Model 2						
Cognitive BDI score	.06	.15	.03	.50	-.03	.52
Somatic BDI score	.08	.063	.09	.028	.09	.028
Women (n=633)						
Model 1						
Continuous BDI score (log10)	.14	.001	.14	<.001	.05	.19
Model 2						
Cognitive BDI score	.09	.023	.06	.10	-.01	.81
Somatic BDI score	.12	.004	.15	<.001	.07	.076

[a] Linear regression analyses adjusted for age, smoking (yes/no), alcohol (excessive usage yes/no), sports (yes/no), and usage of psychotropic drugs (yes/no), diabetes mellitus (DM), cardiovascular disease (CVD), chronic co-morbidity other than DM/CVD (yes/no). BDI= Beck Depression Inventory

in examining the relationship between depression and obesity, the 26 underweight patients were removed from further analyses.

The Pearson correlation coefficient (r) of the BDI sum score (after log-transformation) was 0.42 with the cognitive-affective symptom cluster (p<.001) and 0.81 with the somatic-affective symptoms cluster (p<.001). The different measures of obesity were

strongly correlated with each other; Pearson correlations for BMI and WC 0.80 (p<.001), BMI and WHR 0.38 (p<.001) and WC and WHR 0.78 (p>.001).
As shown in Table 3, the BMI was significantly associated with the BDI sum score (Model 1) and with both the cognitive-affective and the somatic-affective symptom clusters (Model 2). With regard to the measures representing visceral obesity, significant associations were found between WC and WHR and the BDI sum score (Model 1). WC and WHR were specifically associated with the somatic-affective symptom cluster, but not the cognitive-affective symptom cluster (Model 2).

Including interaction terms between all measures of depressive symptoms with sex did not yield significant interaction terms (all p-values > .23). Although the differences between men and women were not statistically different, post hoc analyses showed larger effect sizes for women than for men in all depressive symptoms measures in relation to the BMI and WC, but not the WHR (see Table 3).

Discussion

Main findings
In line with previous findings (de Wit et al, 2009) a U-shaped relationship was found between BMI and depressive symptoms in a population-based sample of people aged 50 to 70. Excluding underweight patients, a positive correlation was found between all different measures of depressive symptoms and BMI, although measures of visceral obesity (WC and WHR), were specifically associated with the somatic-affective symptom cluster. This relationship may suggest an organic etiology of these symptoms of depression.

Relation between obesity (BMI) and depressive symptoms
Recent studies also reported a positive association between depressive symptoms and body mass index (Stunkard et al, 2003; Sachs-Ericsson et al, 2007; de Wit et al, 2010), whereas older studies and studies in specific subgroups defined by ethnicity, sex, age or chronic illness, did not find a relationship or even reported a negative association (Carpenter et al, 2000; Ho et al, 2008). Several explanations can be put forward to explain these discrepancies. First, ignoring the U-shaped association between obesity and depression may easily lead to the conclusion that there is an absent or inverse relationship between depression and obesity. The U-shaped association seems particularly important in the oldest old people because frailty and co-morbidity are associated with depressive symptoms as well as weight loss (Andrew et al, 2007). Second, cultural

aspects and gender differences may account for the psychological sequelae of being overweight. In (some) Eastern cultures obesity is regarded a positive characteristic. In Chinese elderly people, for example, a higher BMI was associated with fewer depressive symptoms (Ho et al, 2008). The opposite seems true for Western countries. Furthermore, in Western societies sex differences may also contribute to sex-specific findings because women are more likely to be stigmatized for being overweight or obese than are men.

Relation between obesity (BMI) and depressive symptom clusters

Separating depressive symptoms into a cognitive-affective and somatic-affective symptom cluster shows that the cognitive symptoms and the somatic symptoms of depression contribute to the relationship between obesity and depressive symptoms. The somatic symptoms accompanying obesity (Dixon et al, 2003) may easily be mixed up with the somatic-affective criteria (fatigue, lack of energy, disturbances in sleep or appetite) of the diagnosis of depression. In the current sample, the somatic-affective symptoms did not entirely explain the relationship between the BMI and general depressive symptoms, because the cognitive-affective symptoms have a significant and independent effect. This is consistent with a recent survey about the association between obesity and depression in middle-aged women that found a strong relationship between obesity and more psychological symptoms such as depressed mood, feelings of guilt or suicidal ideation (Simon et al, 2008). The relationship between BMI and cognitive-affective symptoms may be expected to differ according to gender. In Western cultures, an ideal of slimness in women is associated with elegance, attractiveness, self-control and youth. Studies of self-ratings of attractiveness show that overweight men and women rate themselves as less attractive than to men and women with normal BMI, although men in higher BMI ranges still rate themselves more attractive than do women in these BMI ranges (Weeden et al, 2005). In the current study, the relationship between BMI and cognitive-affective symptoms reached significance only in women.

Relation between visceral obesity and different measures of depression

Depressive symptoms were positively associated with visceral obesity, a more specific risk factor for cardiovascular disease than BMI (Weber-Hamann et al, 2006). Therefore, visceral obesity might be a pathway relating depression to greater incidence rates of cardiovascular disease (Everson-Rose et al, 2009). This is consistent with recent studies showing that obesity and dyslipidemia components of the metabolic syndrome in particular are predictive of depressive symptoms (Akbaraly et al, 2009). Because metabolic disorders and depression are both associated with low-grade systemic inflammation, inflammation may be the mediating mechanism. Inflammation is associated

with the features of sickness behavior, including general weakness, painful symptoms, inability to concentrate and fatigue (Dantzer et al, 2008), that are similar to somatic symptoms in depression.
The somatic-affective symptom cluster rather than the cognitive-affective symptom cluster was related to visceral obesity. Several explanations for this can be put forward. From a psychological perspective, one may hypothesize that feeling guilty about uncontrolled eating habits or inability to keep to a strict diet may be more strongly associated with higher weight (BMI) than with having a "pot-belly" (WC). From a somatic perspective, it may be hypothesized that somatic-affective symptoms are primarily due to a (subclinical) somatic condition or that these symptoms reflect somatic health rather than mental health. The diagnostic criteria of depression would then at least partly confound the prospective role of depression as risk factor for cardiovascular disease (Nicholson et al, 2006). A final potential explanation is that persons with somatic depressive symptoms represent a different subtype of depression. Nevertheless, a recent study showed that depressive symptoms in older people are associated with an increase of visceral fat deposits over time (Vogelzangs et al, 2008). Because these authors made no distinction between specific depressive symptom clusters, it is unknown whether this finding was specifically related to the somatic-affective symptoms of depression and may have been caused by underlying illnesses (e.g. diabetes mellitus).

Methodological considerations
Some limitations of this study have to be acknowledged for proper interpretation. First, the cross-sectional design limits causal interpretation of our findings. In addition to a causal relationship between obesity and depressive symptoms, an underlying latent variable, such as childhood abuse or genetics, may explain both variables (Stunkard et al, 2003) , although the first studies examining a common genetic basis have yielded negative results (Choy et al, 2009).
Second, being a population-based survey some selection might have occurred towards the healthier part of the population. This may account for the relatively low severity of depressive symptoms. Therefore, the findings apply to persons with low depressive symptoms but might not be generalizable to persons with major depressive disorder. Nonetheless, 16.7% of the sample scored on BDI above the cut-off of 10 (Pizzi et al, 2008), whereas meta-analyses show that 13.5% of the population suffers from clinically relevant depressive symptoms, compared to only 9.8% population frequency of minor depression and 1.8% frequency of major depression based on DSM-IV research (Beekman et al, 1999). Although these data suggest a continuum from depressive symptoms to depressive disorders, it is not clear whether this assumption holds true (Beekman et al, 1999). Finally, Computer Tomography was not used at the level of the fourth lumbar

vertebra for quantification of visceral fat (Weber-Hamann et al, 2006).

Clinical implications and future research

Although correlations were of limited size, further research should explore the clinical implications of obesity in patients with depression. Because depression is associated with poorer adherence, interventions for medical problems in obese patients may benefit from effective concurrent treatment of depression (Carpenter et al, 2000). Furthermore, the treatment of obesity itself, including gastric bypass surgery, leads to a decrease in depression (Stunkard et al, 2003). Alternatively the treatment of depression with pharmacotherapeutic agents is often associated with weight gain, whereas cognitive-behavioral therapy is not (Stunkard et al, 2006). In case of co-morbid obesity and depressive symptoms, treatment programs could include a physical exercise program, because this enhances muscle and skeletal strength, decreases obesity and positive affects depression.

References

Everson-Rose SA, Lewis RR, Karavolos K et al. (2009) Depressive symptoms and increased visceral fat in middle-aged women. *Psychosomatic medicine;* 71(40):410-416.

Wouts L, Oude Voshaar RC, Bremmer MA et al. (2008) Cardiac disease, depressive symptoms and incident stroke in an elderly population. *Archives of General Psychiatry;* 65 (5):596-602.

Nicklas BJ, Penninx BW, Cesari M et al. (2004) Association of visceral adipose tissue with incident myocardial infarction in older men and women: the Health, Aging and Body Composition Study. *American Journal of Epidemiology;* 160(8):741-749.

Nicholson A, Kuper H, Hemingway H. (2006) Depression as an etiologic and prognostic factor in coronary heart disease: a meta-analysis of 6362 events among 146 538 participants in 54 observational studies. *European Heart Journal;* 27:2763-74.

Beekman ATF, Copeland JRM, Prince MJ. (1999) Review of community prevalence of depression in later life. *British Journal of Psychiatry;* 174:307-311.

Stunkard AJ, Faith MS, Allison KC. (2003) Depression and obesity. *Biological Psychiatry;* 54 (3):330-337.

Sachs-Ericsson N, Burns AB, Gordon KH et al. (2007) Body mass index and depressive symptoms in older adults: the moderating roles of race, sex, and socioeconomic status. *American journal of Geriatric Psychiatry;* 15(9):815-825.

De Wit LM, van Straten A, van Herten M et al. (2009) Depression and body mass index, a u-shaped association . *BMC public health;* 13:9-14.

Luppino FS, de Wit LM, Bouvy PF et al. (2010) Overweight, Obesity and Depression. A systemic review and meta-analysis of longitudinal studies. *Arch gen psychiatry;* 67(3):220-229.

Carpenter KM, Hasin DS, Allison DB et al. (2000) Relationships between obesity and DSMIV Major depressive disorder, suicide ideation and suicide attempts: results from a general population study. *American Journal of Public Health;* 90(2):251-257.

Ho RC, Niti M, Kua EH et al. (2008) Body mass index, waist circumference, waist-hip ratio and depressive symptoms in Chinese elderly: a population-based study. *International Journal of geriatric psychiatry;* 23(4):401-408.

Schwartz TL, Nihalani N, Virk S et al. (2004) Psychiatric medication-induced obesity: treatment options. *Obesity Reviews;* 5(4):233-238.

Dixon JB, Dixon ME, O/Brien PE. (2003) Depression in association with severe obesity. *Archives of Internal Medicine;* 163:2058-2065.

Villareal DT, Apovian CM, Kushner RF et al. (2005) American Society for Nutrition; NAASO, The Obesity Society. Obesity in older adults: technical review and position statement of the American Society for Nutrition and NAASO, The Obesity Society. *American Journal of Clinical Nutrition;* 82:923-934.

De Jonge P, Ormel J, van den Brink RHS et al. (2006) Symptom dimensions of depression following myocardial infarction and thier relationship with somatic health status and cardio-

vascular prognosis. *American Journal of Psychiatry;* 163:138-144.

Hoogendoorn EH, Hermus AR, de Vegt F et al. (2006) Thyroid function and prevalence of anti-thyroperoxidase antibodies in a population with borderline sufficient iodine intake: influences of age and sex. *Clinical Chemistry;* 52:104–111.

Holewijn S, den Heijer M, van Tits LJ et al. (2010) Impact of waist circumference versus adiponectin level on subclinical atherosclerosis. *J Intern Med;* 267(6):588-98.

Beck AT, Steer RA. (1987) Manual for the Revised Beck Depression Inventory 1. San Antonio, Tex, *Psychological corporation.*

Pizzi C, Manzoli L, Mancini S et al. (2008) Analysis of potential predictors of depression among coronary heart disease risk factors including heart rate variability, markers of inflammation, and endothelial function. *European Heart Journal;* 29 (9):110-117.

Simon GE, Ludman EJ, Linde JA et al. (2008) Association between obesity and depression in middle-aged women. *General Hospital psychiatry;* 30(1):32-39.

Stampfer MJ, Hu FB, Rimm EB et al. (2000) Primary prevention of coronary heart disease in women through diet and lifestyle. *N Engl J Med;* 343:16-22.

Costello A, Osborne J. (2009) Best practices in exploratory factor analysis: four recommendations for getting the most from your analysis. *Practical Assessment Research and Evaluation; 10.* Available online: http://pareonline.net/getvn.asp?v=10&n=7.

Herva A, Laitine J, Miettunen J et al. (2006) Obesity and depression: results from the longitudinal Northern Finland 1966 Birth Cohort Study. *International journal of obesity;* 30 (3):520-7.

Andrew MK, Rockwood K. (2007) Psychiatric illness in relation to frailty in communitydwelling elderly people without dementia: A report from the Canadian Study of Health and Aging. *Canadian Journal of Aging*; 26:33-38.

Weeden J &, Sabini. (2005) J Physical attractiveness and health in Western societies: A review. *Psychological Bulletin;* 131:635-53.

Weber-Hamann B, Werner M, Hentschel F et al. (2006) Metabolic changes in elderly patients with major depression: evidence for increased accumulation of visceral fat at follow-up. *Psychoneuroendocrinology;* 31:347-354.

Akbaraly TN, Kivimäki M, Brunner EJ et al. (2009) Association between metabolic syndrome and depressive symptoms in middle-aged adults: results from the Whitehall II study. *Diabetes Care;* 32(3):499-504.

Dantzer R, O'Connor JC, Freund GG et al. (2008) From inflammation to sickness and depression: when the immune system subjugates the brain. *Nature Reviews Neuroscience;* 9:46-56.

Vogelzangs N, Kritchevsky SB, Beekman ATF et al. (2008) Depressive Symptoms and change in abdominal obesity in older persons. *Archives of general psychiatry;* 65(12):1386-1393.

Choy WG, Lopez-Leon S, Aulchenko YS et al. (2009) Role of shared genetic and environmental factors in symptoms of depression and body composition. *Psychiatric Genetics*; 19(1):32-38.

Waist circumference and Neutrophil Gelatinase-Associated Lipocalin in late-life depression

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Waist circumference and Neutrophil Gelatinase-Associated Lipocalin in late-life depression

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Abstract

Background – Both visceral obesity and depression are associated with impaired health and excess mortality, possibly through overlapping pathophysiological mechanisms like adipose tissue derived inflammatory markers. These results, however, are primarily based on population-based surveys, often restricted to a young population and depression severity scales instead of patients with established diagnosis of depressive disorder.
Methods – We examined the relation between waist circumference and late-life depression using the baseline data of the Netherlands Study of Depression in Older persons (NESDO). Psychopathology has been assessed with Composite International Diagnostic Interview version 2.1.
Results – Adjusted for age, sex, education, lifestyle (smoking, alcohol, physical activity), drug use, cognition and chronic diseases as well as adjusted for body mass index (BMI), analysis of covariance showed that depressed older patients (n=376) had a significantly lower waist circumference (WC) compared to their non-depressed comparisons (n=130): estimated marginal mean (SE) = 93.9 (0.5) versus 97.8 (0.8) cm ($F=15.9$; $df=1,467$; $p<.001$). Multiple linear regression analyses within the depressed group showed that both depression severity (Inventory of Depressive Symptoms) as well as duration-related depression characteristics (age of onset, duration of illness, life-time comorbid dysthymia) were associated with the WC. Only the severity of depressive symptoms remained significant after further adjustment for the BMI. Interestingly, a recently discovered adipokine, Neutrophil Gelatinase-Associated Lipocalin (NGAL), was associated with late-life depression, but only in the subgroup of patients with a pathologically increased WC.
Conclusions – Population-based findings on the positive association between obesity and depressive symptoms can thus not be generalised to a clinical sample of depressed older patients. The impact of the WC on course and treatment outcome of late-life depression should be examined in clinical samples, taken into account the relative impact of the WC in proportion to the general level of obesity as indexed by the BMI and the role of adipokines.

Keywords

Waist circumference, Obesity, late-life Depression, Neutrophil Gelatinase-Associated Lipocalin

Introduction

Depression and obesity are two major risk factors for unfavourable health outcomes (Penninx et al, 2001; Everson-Rose et al, 2009). Meta-analysis of cross-sectional studies has confirmed a significant association between depression and obesity (de Wit et al, 2010). Subsequently, meta-analyses of longitudinal studies identified depression as a risk factor for weight gain, as well as obesity as a risk factor for the development of depression (Luppino et al, 2010). Current hypotheses about predisposition of depression to obesity include neuroendocrine disturbances in the Hypothalamic Pituitary Adrenal Axis (HPA-axis) (Deushle et al, 1998) changing lifestyle factors as eating patterns and reduced physical activity (Stunkard et al, 2003) and the use of antidepressants (Schwartz et al, 2004). Biological mechanisms like HPA-axis dysregulation (Pasquali 2012; van Reedt Dortland et al, 2012) but also psychological mechanisms like stigmatization, negative body image and disappointment about failing diets (Dixon et al, 2003) are hypothesized to predispose obese people to depression. In addition to these hypotheses, inflammatory pathways have gained increasing attention and may explain the bi-directional association between depression and obesity (Bremmer et al, 2008; Milaneshi et al, 2012; Daly et al, 2013).

Despite well conducted longitudinal studies on the relationship between depression and obesity, important clinical aspects remain unknown. Firstly, only three longitudinal studies in the above-described meta-analyses were conducted in an older cohort (Roberts et al, 2003; Sachs-Ericson et al, 2007; Vogelzangs et al, 2008). These three studies also suggested a bidirectional association between depression and obesity in later life, although only one of these studies reported statistically significant results (Roberts et al, 2003; Sachs-Ericson et al, 2007; Vogelzangs et al, 2008). More recent (and cross-sectional) population-based studies in older people have even reported a negative association, i.e. lower body weight in depression (Ho et al, 2008; Wong et al, 2011; Dong et al, 2012). Secondly, it is unknown whether depressive symptoms measured in population-based studies can be generalised to clinical samples of depressed patients. With one exception, all studies have been conducted in population-based samples, the vast majority in an adult population (de Wit et al, 2010; Luppino et al, 2010; Marijnissen et al, 2011; Arterburn et al, 2012). Recently, the first study in a clinical sample confirmed that depressive disorder is associated with an increase in abdominal obesity over time (Van Reedt Dortland et al, 2013). This study was limited to patients aged below 65 years. Whether these findings also account for older persons remains unclear. In late-life depression an absent or even inverse association might be hypothesized

as in later life the prevalence of physical frailty sharply increases with age (Collard et al, 2012) and physical frailty is associated with both underweight and depression (Fried et al, 2001; Collard et al, 2013).

Furthermore, it is important to consider the definition of obesity and depression. Depression has been specifically linked with visceral fat accumulation (Vogelzangs et al, 2008). A study on the prospective impact of the metabolic syndrome in adults has identified waist circumference as the most important component predicting the onset of depression in non-depressed persons and a protracted course in depressed patients (Vogelzangs et al, 2011). Despite the presence of diagnostic criteria, depressive disorder is a heterogeneous syndrome. Recently, in a large population based study among middle-aged and older persons, we found that depressive symptoms were positively associated with both body mass index and waist circumference. Interestingly, the cognitive-affective symptoms of depression were associated with both the increased body mass index and increased waist circumference, whereas the somatic-affective symptoms of depression were specifically associated with the increased waist circumference (Marijnissen et al, 2011; Marijnissen et al, 2013).

The waist circumference is often used as a proxy for visceral adipose tissue. Visceral fat is a metabolically active tissue secreting cytokine-family proteins, collectively called adipokines (Trujillo et al, 2006; Milaneshi et al, 2012; Zhao et al, 2013). Such adipokines are hypothesised to induce a chronic low-grade inflammatory environment, thus contributing to the negative health effect of obesity. Neutrophil Gelatinase-Associated Lipocalin (NGAL), also called Lipocalin-2, is a recently identified adipokine with high levels of expression and secretion in the white adipose tissue (Huang et al, 2012). Interestingly, induction of a peripheral inflammatory response as well as psychological stressors induces cerebral NGAL expression (Ip et al, 2011; Mucha et al, 2011), which consequently can reduce hippocampal synaptic spine density (Mucha et al, 2011). We recently showed that NGAL expression can induce a pro-apoptotic signaling cascade by attenuating Akt phosphorylation of the protein kinase B (PKB)/Akt pathway and sensitize neurons to beta-amyloid induced cell death (Naudé et al, 2012). Cellular signaling via Akt has been postulated as a key pathway involved in neuroplasticity in the hippocampus (Balu et al, 2012; Jin et al, 2012). Interestingly the PKB/Akt activity is also decreased in post mortem human brain tissue of suicide victims compared to non-depressed controls (Karege et al, 2011). These data collectively suggest that increased central nervous system NGAL levels can lead to reduced neuroplasticity. Plasma levels of NGAL appear to be increased in depressed older persons (Naudé et al, 2013) as well as obese people (Auget et al, 2010; Huang et al, 2012). Animal models have further shown that NGAL plays a functional role in systemic insulin sensitivity and glucose homeostasis (Wang et al, 2007). As with leptin (Milaneschi et al, 2012), the

presence of increased NGAL levels in obese persons may be considered as an indicator of NGAL resistance. If true, the risk for the onset of depression would be especially increased in persons with high levels of NGAL and visceral fat.

The primary objective of the present study was to examine the association between depression and waist circumference in an older (≥ 60 years) depressed sample and to explore several characteristics of late-life depression within this association. Our second objective is to explore the role of NGAL. Being an adipokine, we hypothesise that increased NGAL levels are associated with depression, especially in persons with an increased waist circumference as proxy for visceral obesity.

Methods

Sample

For the present study, we used the baseline assessment of the Netherlands Study of Depression in Older persons (NESDO) (see Comijs et al, 2011). NESDO is an on-going cohort study designed to examine the determinants of the course and consequences of depressive disorders in older persons, including 378 depressed and 132 non-depressed older persons. Recruitment of depressed older persons took place in five regions in the Netherlands from both mental health care institutes and general practitioners in order to include persons with late-life depression in various developmental and severity stages. Persons with a primary diagnosis of dementia, a Mini Mental State Examination-score (MMSE) under 18 (out of 30 points) (Folstein et al, 1975), and insufficient command of the Dutch language were excluded. The comparison group of non-depressed persons was recruited at the same general practices that recruited patients. A random sample of older people who scored less than four on the Geriatric Depression Scale during a visit to their GP was asked informed consent. Exclusion criteria were a lifetime diagnosis of depression, dementia or other serious psychiatric disorders, and insufficient command of the Dutch language.

Data collection of the baseline assessment started in 2007 and was finished in September 2010. The baseline assessment included written questionnaires, interviews and physical assessments. Interviews were audio taped to control the quality of the data. The ethical review boards of the participating institutes have approved this study. All participants gave informed consent after oral and written information about the study. Of the 510 participants in NESDO, 4 participants were excluded because of missing body mass index (n=1) and missing waist circumference (n=3). This left a final study sample of 506 people (376 depressed and 130 non-depressed).

With respect to the second objective, a further 12 participants (9 depressed, 3 non-depressed) were excluded due to refusing or failing blood withdrawal. Thus, analyses on NGAL/Lipocalin2 are based on 494 participants (367 depressed patients and 127 non-depressed controls).

Variables of interest

Depression diagnoses - The past 6-month diagnosis of depression and dysthymia according to DSM-IV-R criteria (APA, 2000) were assessed with the Composite International Diagnostic Interview (CIDI; WHO version 2.1; 12 month version, 1997). The CIDI is a structured clinical interview that is designed for use in research settings and has high validity for depressive and anxiety disorders (Wittchen et al, 1991; Kessler et al, 2010). As in NESDA (The Netherlands Study of Depression and Anxiety; Penninx et al, 2008), we added questions to determine the research DSM-IV diagnosis of current minor depression (Comijs et al, 2011). Among the depressed sample, 357/376 (94.9%) met criteria for a major depressive disorder (MDD) with the past 6 months, 20 (5.3%) for a current minor depression and 100 (26.6%) for dysthymia (in the past-six months). Due to double diagnoses, numbers do not add up to 100%.

Depression characteristics - Characteristics of depression will be categorised in those characteristics indicative of a prolonged or chronic course (duration related measures) and those indicative of a more severe episode (severity related measures) as indicated in Table 4.

Duration-related measures - Based on data from the CIDI-interview, we assessed additional age of onset of depression (age of the participant at the time of the first depressive episode), recurrence (presence of depressive episode prior to the current episode) and life-time dysthymia.

Severity related measures - Severity of depression was measured by the 30-item selfrating Inventory of Depressive Symptomatology (IDS), which has adequate psychometric properties (Rush et al, 1996). The sum score ranges from 0 to 60; the severity of depression can be classified as none (score range 0 through 12), mild (13 through 24), moderate (25 through 37), severe (38 through 47) and very severe (48 or higher). To examine different symptom dimensions of late-life depression, three symptom profiles of the IDS were used, a mood, motivation and somatic dimension. These three homogenous symptom dimensions were shown to have a good fit with exploratory and confirmatory factor analysis in the NESDO study (Hegeman et al, 2012).

Obesity - Waist circumference was measured at the level of the umbilicus (cm). According to the National Cholesterol Education Program (NCEP)-Adult Treatment Panel III, a waist

circumference above 88 cm and 102 cm is considered pathologically increased in females and males, respectively (Alexander et al, 2003). In addition, standardized assessments of weight (kg) and height (m) were used to calculate the body mass index (weight (kg) divided by the square of the height (m^2)).

NGAL measurement in plasma by ELISA - Quantification of NGAL from plasma was performed via a constructed sandwich ELISA using human Lipocalin-2/NGAL ELISA capture antibody (R&D Systems), recombinant human Lipocalin-2/NGAL (R&D Systems) for the internal standard and biotinylated human Lipocalin-2/NGAL detection antibody (R&D Systems). Plasma was diluted 1:100. A blinded ELISA analysis was performed on coded samples. Briefly, plates (96 wells, Maxisorb, Nunc) were coated with the capture antibody (100 µl; 2 µg/ml) diluted in phosphate buffered saline (PBS, pH 7.4). After overnight incubation at room temperature, the coated plates were washed with Tris Buffered Saline (TBS) containing 0.05% Tween 20 (TBS/T) and nonspecific binding sites blocked by incubation with 300 µl of PBS containing 1% Bovine Serum Albumin (BSA) (PBS/BSA) for 2 hours at room temperature on a shaker. After washing, 100 µl of either the standards (recombinant human NGAL) or samples, diluted in PBS/BSA were added to the plates and incubated for 2 hours at room temperature on a shaker. Plates were washed six times and 100 µl of biotinylated human Lipocalin-2/NGAL detection antibody (100 ng/ml) diluted in PBS/BSA was added. After 2 hours on a shaker at room temperature, plates were washed six times and incubated with 100 µl Avidin-horseradish peroxidase (eBioscience) in PBS/BSA (1:1000) for 20 minutes on shaker at room temperature. Plates were then washed six times and 100 µl of substrate solution containing 1mg/ml of O-phenylenediamine (Sigma) in 0.05M citric acid sodium phosphate Buffer (pH 5.0) with hydrogen peroxide (0.06%) was added. The reaction was stopped by adding 100 µl of a 3N HCl solution. The absorbance was determined at 492 nm with background subtraction at 620 nm using an ELISA reader (Asys UVM 340, Biochrom, Cambridge, UK). The quantity of NGAL was estimated from the calibration curve which ranged from 78 to 5000 pg/ml. Samples were stored at -80 °C. Blood samples were collected in the morning to standardize for collection time. The intra- and inter-assay coeeficients of variation were 3% and 5%, respectively (Comijs et al, 2011; see Naudé et al, 2013).

High-sensitivity C-reactive protein - In addition to NGAL levels, high-sensitivity plasma levels of CRP were measured in duplicate by a immunoturbidimetric assay (Tina-quant CRPHS, Roche Diagnostics, Mannheim, Germany) at the Clinical Chemistry department of the VU University Medical Center). Intra- and inter-assay coefficients of variation were 2% and 2%. As CRP levels were positively skewed, ln-transformed values

were used to normalize the distribution when included in the multivariate analyses.

Covariates

In addition to age, sex and years of education (first set of confounders), we *a priori* considered the following potential confounders based on their relationship with both depression and obesity.

The second set of confounders included lifestyle factors like smoking, use of alcohol, physical activity and use of antidepressants (Schwartz et al, 2004). Smoking was defined as currently smoking (yes/no). Based on the first two questions of the Alcohol Use Disorders Identification Test (AUDIT) (Babor et al, 2001; Aalto et al, 2011), we classified alcohol consumption in three categories according to the average number of units taken on a typical drinking day and the frequency of drinking: 1) no drinking, 2) moderate alcohol use, and 3) severe alcohol use. Severe alcohol use was defined as taking 5 – 10 units on a typical drinking day irrespective of the frequency of drinking or 3 or 4 units on a typical drinking day at least 4 or more days a week. Moderate alcohol use was defined as any alcohol use not being severe use. Physical activity was measured with the last-seven-days short-form (8-items) of the self-administered version of the International physical Activities Questionnaire (IPAQ). Psychometric properties of the long and short version of the IPAQ are acceptable (Craig et al, 2003). The physical activity was classified in three categories (minimal, moderate, high).

Medication use was assessed based on drug container inspection of all drugs used in the past month and classified according to the World Health Organization Anatomical Therapeutic Chemical classification (ATC) (WHO, 2012). Medication was only considered when taken on a regular basis (at least 50% of the time). For the present study, we took antidepressant drugs and anti-inflammatory drugs into account. Antidepressant medication included selective serotonin reuptake inhibitors (SSRIs) (N06AB), serotonin-norepinephrine reuptake inhibitors (SNRI) (N06AX16, N06AX21), tricyclic antidepressants (TCAs)(N06AA) and tetracyclic antidepressants (TeCA) (N06AX03, N06AX05, and N06AX11). Anti-inflammatory drugs included amino salicylic acid and similar agents (A07EC), anti-allergic agents (A07EB), systemically applied corticosteroids (H02A), anti-inflammatory and anti-rheumatic products (M01) and other analgesics and antipyretics (N02B).

The third set of confounders consisted of parameters of physical functioning and included cognitive functioning and the number of chronic diseases. Cognitive functioning was assessed by the Mini Mental State Examination (MMSE) (Folstein et al, 1975). The MMSE score ranges from 0-30, with higher scores indicating better cognitive functioning.

The number of chronic diseases was assessed by means of a self-report questionnaire that has previously been used in NESDA (Penninx et al, 2008). The participants were

asked whether they currently or previously had any of the following chronic diseases or disease events: cardiac disease (including myocardial infarction), peripheral atherosclerosis, stroke, diabetes mellitus, COPD (asthma, chronic bronchitis or pulmonary emphysema), arthritis (rheumatoid arthritis or osteoarthritis) or cancer, or any other disease. Compared to general practitioner information, the accuracy of self-reports of these diseases was shown to be adequate and independent of cognitive impairment (Kriegsman et al, 1996).
In case of associations tested with NGAL or hsCRP, having had a cold or fever in the previous week to blood withdrawal (yes/no) was also taken into account.

Statistical methods
Waist circumference was compared between depressed and non-depressed persons with ANCOVA adjusted for different sets of covariates (model 1: age, gender, level of education; model 2: additionally adjusted for cognitive functioning, chronic diseases and antidepressant drug use; model 3: additionally adjusted for lifestyle characteristics including smoking, alcohol use and physical activity). Subsequently, in model 4 the analysis was additionally corrected for body mass index in order to examine the impact of the waist circumference when adjusted for general obesity.
In order to examine a potentially moderating role of obesity in the association between NGAL and depression, multiple logistic regression analyses were conducted with depression (yes/no) as dependent variable adjusted for the covariates described above, added with having had a cold or fever in the previous week to blood withdrawal. Waist circumference and plasma NGAL levels will be included as independent variables. In these models, the interaction between NGAL and waist circumference will be tested and in case of significance, analyses will be presented separately for participants with and without a pathologically increased waist circumference.
Subsequently, multiple linear regression analyses in the depressed subgroup were conducted with waist circumference as dependent variable and depression severity characteristics (IDS sum score, IDS-mood subscale, IDS-motivation subscale and IDS-somatic subscale) as well as duration related characteristics (age of onset, duration of illness, life-time comorbidity with dysthymia) as independent variables in separate models. These analyses were fully adjusted for the covariates described above.
Finally, a moderating role of plasma NGAL in the association between obesity and depression characteristics will be examined by adding the interaction term between NGAL and a specific depression characteristic to the fully adjusted linear regression models described above.
Finally, all analyses were rerun replacing NGAL levels by hsCRP levels, in order to examine whether results were indeed specific for NGAL and not a none-specific

inflammatory reaction.
By convention, p-values below .05 will be considered statistically significant for individual variables, whereas p-values below .10 will be considered statistically significant for interaction terms. All analyses were performed in SPSS version 18.0 (Inc. Chicago).

Results

Obesity in depressed versus non-depressed persons
Table 1 presents the characteristics of the study population. Depressed patients and the non-depressed comparison group did not differ with respect to the body mass index (26.3 (SD=4.4) versus 27.0 (SD=4.1), t=1.6, df=504, p=.121), whereas depressed persons had a significantly lower waist circumference (93.5 (SD=13.0) versus 98.4 (SD=15.3), t=3.5, df=504, p=.001).
As shown in Table 2, the difference in waist circumference between depressed and non-depressed persons became more significant when adjusted for covariates, and also remained significant after adjustment for body mass index (estimated marginal mean (SE) = 93.9 (0.5) versus 97.8 (0.8); F=15.9; df=1,467; p<.001).

As these results were contrary to our hypothesis that an increased waist circumference would be found in depression post-hoc analyses were conducted excluding depressed patients that reported depression related weight loss in the past 2 years based on the corresponding CIDI question (n=131). These analyses yielded almost comparable results. In the fully adjusted models, depressed older persons still had a significantly lower waist circumference compared to the non-depressed comparison group (94.3 (SE=0.9) versus 100.2 (SE=1.3); F=13.0, df=1,340; p< .001), which also remained significant after adjustment for body mass index (95.0 (SE=0.6) versus 98.8 (SE=0.9); F=12.5, df=1,339; p< .001).

Impact of obesity on the association between NGAL and depression status
In a previous paper of the present sample, we already showed that depression is associated with increased NGAL levels (see Naudé et al, 2013). In order to examine whether the association between NGAL and depression status (yes/no) is conditional on the waist circumference, we examined the interaction term between NGAL level and waist circumference in a logistic regression model adjusted for all confounders, with depression status as the dependent variable. The interaction term between NGAL and waist circumference was significant irrespective of adjustment for body mass index. Without adjusting for body mass index the OR of waist circumference by NGAL was

Table 1 Characteristics of depressed patients and their non-depressed comparison group (n=506).

Characteristics		Depressed patients (n=376)	Non-depressed controls (n=130)	Statistics
Depressive symptom severity (IDS)	Mean (SD)	30.0 (13.0)	7.6 (5.7)	T=-18.9, df=496, p<.001
Plasma NGAL levels (pg/ml)	Mean (SD)	62.00 (23.30)	53.25 (21.29)	T=-3.7, df=492, p<.001
High-sensitivity CRP levels	Median (IQR)	1.88 (3.18)	1.59 (2.28)	T=-1.4, df=486, p=.166*
Demographics				
• Age	Mean (SD)	70.7 (7.4)	69.9 (7.0)	T=-1.1, df=504, p=.267
	(range)	60 - 90)	(60 - 93)	
• Female sex	n (%)	248 (66.0)	80 (61.5)	χ^2=0.8, df=1, p=.363
• Years of education	Mean (SD)	10.5 (3.4)	12.5 (3.5)	T=5.8, df=504, p<.001
Somatic status				
• Global cognitive	Mean (SD)	27.7 (2.0)	28.4 (1.6)	T=3.3, df=503, p=.001
functioning (MMSE)				
• No. of chronic diseases	Mean (SD)	2.1 (1.5)	1.5 (1.1)	T=-4.5, df=503, p<.001
• Use of antidepressants	n (%)	272 (72.3)	3 (2.3)	χ^2=191, df=1, p<.001
• Waist circumference (cm)	Mean (SD)	93.5 (13.0)	98.4 (15.3)	T=3.5, df=504, p=.001
• Body Mass Index	Mean (SD)	26.3 (4.4)	27.0 (4.1)	T=1.6, df=504, p=.121
Life-style characteristics				
• Alcohol use				χ^2=36.2, df=2, p<.001
o No use	n (%)	148 (40.0)	16 (12.7)	
o Moderate usage	n (%)	189 (51.1)	84 (66.7)	
o Severe usage	n (%)	33 (8.9)	26 (20.6)	
• Smoking	n (%)	99 (26.5)	10 (7.7)	χ^2=20.2, df=1, p<.001
• Physical activity				χ^2=9.0, df=2, p=.011
o Low	n (%)	113 (31.0)	22 (17.3)	
o Medium	n (%)	138 (38.8)	55 (43.3)	
o High	n (%)	114 (31.2)	50 (39.4)	

* T-test on ln-transformed values

1.001 [95% CI = 1.000 – 1.002], p=.093; when additional adjusting for body mass index the OR of waist circumference by NGAL was 1.001 [95% CI: 1.000 – 1.002], p=.072. Therefore, subsequent analyses will be presented separately for participants with nor-

mal and pathological increased waist circumference (Table 3). As shown in Figure 1, NGAL plasma levels are only elevated in depressed older patients with a pathologically increased waist circumference.

HsCRP levels (see Table 1 for unadjusted results) did not differ between patients and controls in the fully adjusted models (p=.482). Moreover, these results were not conditional on the WC as indicated by non-significant interaction terms between hsCRP and WC when predicting depression status (p=.684 not adjusted for BMI; p=.649 adjusted for BMI)

Table 2 Differences in obesity measures by depression status (ANCOVA[a]).

Measures of obesity	Depressed patients (n=376) Adjusted Mean (SD)	Non-depressed controls (n=130) Adjusted Mean (SD)	Statistics
Body Mass Index (BMI)			
• Model 1 (+socio-demographics)	26.6 (0.2)	27.2 (0.4)	F=5.02, df=1,501, p=.025
• Model 2 (+physical functioning)	26.2 (0.2)	27.5 (0.4)	F=8.74, df=1,498, p=.003
• Model 3 (+life-style)	26.2 (0.2)	27.5 (0.4)	F=7.63, df=1,468, p=.006
Waist circumference (WC)			
• Model 1 (+socio-demographics)	93.4 (0.7)	98.8 (1.2)	F=15.82, df=1,501, p<.001
• Model 3 (+physical functioning)	93.1 (0.7)	99.5 (1.2)	F=21.42, df=1,498, p<.001
• Model 4 (+life-style)	93.1 (0.7)	100.1 (1.3)	F=22.20, df=1,468, p<.001
• Model 4 (+BMI)[b]	93.9 (0.5)	97.8 (0.8)	F=15.92, df=1,467, p<.001

- Model 1: Adjusted for age, gender and level of education (ANCOVA, shown are adusted means (SEM))
- Model 2: Additionally adjusted for global cognitive functioning (MMSE), no. of chronic diseases, use of antidepressants
- Model 3: Additionally adjusted for lifestyle, i.e. alcohol use (no, moderate, severe), smoking (yes/no), physical activity (minimal, moderate, high).
- Model 4: Additionally adjusted for BMI

[a] Please note that differences are not controlled for antidepressant drug use (as only 3 controls use anti-depressants):
- o Firstly, among depressed patients, antidepressant drug use was not associated with obesity in fully adjusted models comparing depressed patients without and with antidepressants (for WC: EM(SE) = 93.4 (1.2) versus 93.6 (0.8), F=0.03; df=1,345; p=.875; for BMI (EM(SE) = 26.4(0.4) versus 26.4(0.3), F=0.01, df=1,345, p=.915).
- o Secondly, results did not differ by antidepressant drug class (SSRI, TCA, other); for WC: F=1.08, df=3.320, p=.359; for BMI: F=1.43, df=3,320, p=.235.

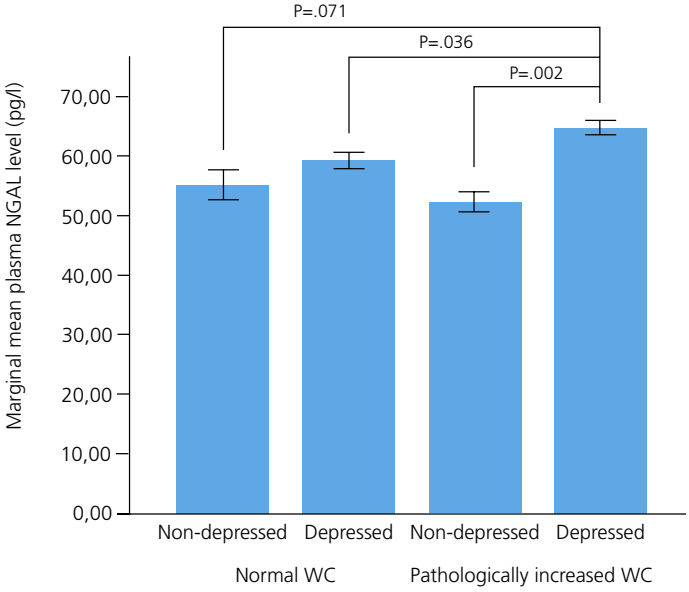
[b] The BMI was not significant anymore in this latter model.

Table 3 Odds of NGAL on depression status (yes/no).

	Not adjusted for BMI OR [95% CI][a]	*p*	Adjusted for BMI[b] OR [95% CI][a]	*p*
Whole sample (n=506)				
• Waist circumference	0.946 [0.925 – 0.967]	<.001	0.928 [0.895 – 0.963]	<.001
• Plasma NGAL level	1.015 [1.003 – 1.028]	.018	1.015 [1.003 – 1.028]	.016
Normal wc				
• Waist circumference	0.897 [0.828 – 0.972]	.008	0.912 [0.834 – 0.998]	.045
• Plasma NGAL level	0.998 [0.977 – 1.020]	.843	0.999 [0.977 – 1.021]	.899
Pathologically increased wc				
• Waist circumference	0.959 [0.923 – 0.997]	.033	0.927 [0.878 – 0.978]	.006
• Plasma NGAL level	1.023 [1.006 – 1.041]	.007	1.025 [1.007 – 1.042]	.006

[a] All models are adjusted for age, sex, educational level, cold or fever in the week previous to blood withdrawal (yes/no), no. of chronic disease, global cognitive functioning (MMSE), smoking (yes, no), alcohol use (no, moderate, severe) and physical activity (low, moderate, high), antidepressant drug use (SSRI, TCA, Other), anti-inflammatory drugs (yes/no).
[b] The BMI was not significant anymore in any of these models.

Figure 1 Plasma NGAL levels by waist circumference and depression status.*



* Overall, fully adjusted ANCOVA: F=3.54, df=3,462; p=.015

Characteristics of obesity in depressed persons
Linear regression analyses in the depressed subgroup (n=376) showed that increased waist circumference was associated with both depression severity measures as well as duration related characteristics (Table 4). When additionally adjusted for body mass index, the strength of the association decreased, but the IDS sum score as overall severity measure remained significantly associated (B=0.06 (0.03), β=0.06, p=.046), whereas the motivation subscale became significant (B=0.26(0.13), β=0.06, p=.050).

Does NGAL moderate the association between depression characteristics and obesity
Among the subgroup of depressed older persons, NGAL is associated with the waist circumference in fully adjusted linear regression models (B(SE)=0.082 (0.030), β=.15; p=.006).

Table 4 Determinants of WC in depressed patients separate, fully adjusted linear regression models.*

Determinant	Waist Circumference (WC)					
	Not adjusted for BMI			Adjusted for BMI[a]		
	B (SE)	*β*	*p*	B (SE)	*β*	*p*
Depression severity measures						
• IDS sum score	0.11 (0.06)	.11	.046	0.06 (0.03)	.06	.046
• IDS, mood subscale	0.32 (0.14)	.13	.023	0.12 (0.08)	.05	.131
• IDS, motivation subscale	0.41 (0.23)	.10	.077	0.26 (0.13)	.06	.050
• IDS, somatic subscale	0.16 (0.17)	.05	.355	0.09 (0.10)	.03	.367
Duration related disease characteristics						
• Age of onset (in years)	-0.08 (0.04)	-.13	.024	-0.01 (0.02)	-.02	.579
• Age of onset (<> 60 years)	-4.04 (1.50)	-.15	.007	-1.21 (0.85)	-.04	.155
• Life-time comorbidity with dysthymia	4.40 (1.40)	.16	.002	0.59 (0.81)	.02	.469
• Duration of illness (years)	0.08 (0.04)	.12	.024	0.02 (0.02)	.02	.455

* All models are adjusted for age, sex, educational level, no. of chronic disease, global cognitive functioning (MMSE), smoking (yes, no), alcohol use (no, moderate, severe) and physical activity (low, moderate, high), antidepressant drug use (SSRI, TCA, Other), anti-inflammatory drugs (yes/no).

[a] The BMI was not significant in any of these models.

Table 5 Association between NGAL and waist circumference by different classes of depression severity and by the presence of life-time dysthymia using multiple linear regression analyses.*

Determinant	Waist Circumference (WC)		
	B (SE)	*β*	*p*
Severity of depression			
Not additionally adjusted for BMI			
• No/mild depression	-0.01 (0.04)	-.02	.775
• Moderate depression	0.04 (0.05)	.07	.449
• (Very) severe depression	0.16 (0.07)	.27	.021
Additionally adjusted for BMI[a]			
• No/mild depression	0.01 (0.03)	.02	.686
• Moderate depression	0.01 (0.03)	.01	.858
• (Very) severe depression	0.12 (0.03)	.19	.001
Life-time history of dysthymia			
Not additionally adjusted for BMI			
• No life-time dysthymia	<0.01 (0.03)	.01	0.906
• Life-time dysthymia	0.19 (0.06)	.34	.001
Additionally adjusted for BMI[a]			
• No life-time dysthymia	0.02 (0.02)	.04	.366
• Life-time dysthymia	0.11 (0.03)	.20	.001
Age of onset depression			
Not additionally adjusted for BMI			
• Early onset depression (<60 years)	0.05 (0.04)	.08	.291
• Late-onset depression (≥60 years)	0.11 (0.05)	.23	.019
Adjusted for BMI[a]			
• Early onset depression (<60 years)	0.07 (0.02)	.11	.002
• Late-onset depression (≥60 years)	0.07 (0.03)	.15	.025
Duration of illness (median split at 19 years)			
Not additionally adjusted for BMI			
• Short duration of illness (≤19 years)	0.11 (0.04)	.24	.003
• Long duration of illness (>19 years)	0.03 (0.05)	.04	.624
Adjusted for BMI[a]			
• Short duration of illness (≤19 years)	0.08 (0.02)	.16	.002
• Long duration of illness (>19 years)	0.08 (0.03)	.12	.004

* All models are adjusted for age, sex, educational level, cold or fever in the week previous to blood withdrawal (yes/no), no. of chronic disease, global cognitive functioning (MMSE), smoking (yes, no), alcohol use (no, moderate, severe) and physical activity (low, moderate, high), antidepressant drug use (SSRI, TCA, Other), anti-inflammatory drugs (yes/no).

[a] The BMI was not significant in any of these models.

First, we examined which depression characteristics (see Table 4) that were associated with waist circumference interacted with plasma NGAL level. Not adjusted for the body mass index, NGAL interacted with the IDS sum score (B(SE)=0.004 (0.002), β=0.35, p=.019), IDS mood scale (B(SE)=0.012 (0.004), β=0.36, p=.009), IDS motivation scale (B(SE)=0.015 (0.008), β=0.29, p=.046), age of onset (continuous: B(SE)=0.002 (0.001), β=.33, p=.086; dichotomised: B(SE)=0.12 (0.06), β=.43, p=.053), with life-time dysthymia (B(SE)= 0.16 (0.06), β =0.34, p=.009), and with duration of illness (B(SE)= -0.003 (0.001), β=-.30, p=.057) when predicting the waist circumference in depressed older persons. Interaction between NGAL and other depression characteristics were not significant (all p-values >.10).

Adjusted for body mass index, five depression characteristics interacted with plasma NGAL levels when predicting waist circumference in depressed older persons. The significant interaction terms included NGAL by IDS total score (B(SE)=0.003 (0.001), β=.27, p=.006), NGAL by IDS mood subscale (B(SE)=0.009 (0.003), β =.26, p=.003), IDS motivation scale (B(SE)=0.011 (0.005), β=0.20, p=.031), IDS somatic scale (B(SE)=0.007 (0.004), β=0.20, p=.051) and finally NGAL by life-time dysthymia ((SE)=0.103 (0.040), β =.22, p=.011). Table 5 presents the results split by depression severity, life-time dysthymia, age of onset and duration of illness. Results by depression severity will be presented for three severity groups, i.e. none or mild symptoms, moderate symptoms, and severe/very severe depressive symptoms, respectively.

Finally, a similar approach was applied with respect to hsCRP levels. However, all results appeared to be non-significant.

Discussion

Main findings

Depressed patients aged 60 years and over were significantly less obese than the non-depressed comparison group (see Table 2). Population-based findings of a positive correlation between obesity and depressive symptoms can thus not be generalised to patients suffering from late-life depression. The difference with respect to the waist circumference remained even significant after adjustment for the body mass index. Interestingly, the association between increased Neutrophil Gelatinase-Associated Lipocalin (NGAL) levels and depression, recently reported by our group (Naudé et al, 2013) appears to be driven by a pathologically increased waist circumference. Increased NGAL levels may thus be only relevant in a subgroup of depressed older patients.

Obesity in late-life depression

Although most studies report a positive association between obesity and more severe depressive symptoms (as confirmed by meta-analyses), absence or even inverse relationships in this association as found in our study have been reported before (Ho et al, 2008; Wong et al, 2011; Dong et al, 2012). A closer look at these contradictory findings, shows that a negative association between depression and obesity has primarily been reported in an older, Asian population (Ho et al, 2008; Wong et al, 2011; Dong et al, 2012). In eastern cultures, obesity is regarded as a positive characteristic. As 95% (464/489) of our participants are from a north-European ancestry, this cannot be an explanation for our findings. Our sample further differs from population-based studies by having included a relatively severe group of depressed patients meeting the DSM-IV-TR criteria for depression or dysthymia. This is in contrast to population-based studies where severe cases are underrepresented by selection bias (Marijnissen et al, 2011) and results are generally based on depression severity scales (de Wit et al, 2010; Luppino et al, 2010). The only study on a clinical sample (aged 18-65 years old) thus far has confirmed the meta-analytic results of population-based studies (van Reedt Dortland et al, 2013). As this study has applied a similar study design as we did (see Penninx et al. 2008; Comijs et al, 2011), our results cannot simply be explained by having a clinical sample of depressed patients. Our data thus suggest that the relationship between obesity and depression may be different across the lifespan. Although tentative, it may be that depressed older persons have more often lost weight due to comorbid physical frailty or somatic comorbidity, which in itself is associated with depression (Andrew et al, 2007; Collard et al, 2013). Moreover, even aging in general has already been associated with nutritional deficiencies that may also contribute to depressive symptoms (de Boer et al, 2013). Another explanation could still be significant weight loss during the actual depressive episode. Nonetheless, this is unlikely as our post-hoc analyses excluding the patients with significant and unintended weight loss in the past two years yielded similar results. Moreover, this explanation also does not explain why the waist circumference is specifically affected relative to the body mass index.

Within the depressed group, characteristics of a more severe depressive episode as well as a longer history of depression were associated with a higher waist circumference. When adjusted for body mass index, only the association between waist circumference and overall depression severity remained significant, in contrast to the depression duration related characteristics which all lost significance. This may indicate that variance in waist circumference adjusted for general obesity may specifically affect actual depression severity. A possible explanation may lie in the metabolic activity of the visceral fat tissue (Trujillo et al, 2006). Interestingly, inflammatory markers have been specifically related with features of sickness behaviour, including general

weakness and fatigue (Dantzer et al, 2008).

Adipokines and late-life depression

Depression has increasingly been linked with visceral fat accumulation (Vogelzangs et al, 2008) as well as low-grade systemic inflammation (Dowlati et al, 2008; Howren et al, 2009). Visceral fat tissue is metabolic active by the secretion of both pro- and anti-inflammatory cytokines, collectively called the adipokines. Although NGAL has not been studied previously in the association between obesity and depression, comparable results have been found for other adipokines. In older men, high leptin has been associated with an increased onset of depressive symptoms in the presence of abdominal obesity (Milaneshi et al, 2012). The fact that NGAL exerts its effects primarily in case of a pathologically increased waist circumference, contributes to its role as an adipokine. Adipokines have indeed been specially associated with visceral obesity. For example, plasma levels of adiponectin, a protective cytokine for vascular health, are lowered in case of visceral obesity resulting in negative health effects independent of the body mass index (Mathieu et al, 2009; Taylor et al. 2010; Matsuzawa et al, 2012).

Methodological considerations

The strengths of our study are the large number of older persons suffering depression and the comprehensive assessment of depression characteristics and confounding factors. However, some limitations should be acknowledged for proper interpretation. Firstly, the cross-sectional study design precludes causal interpretations of the findings. Secondly, plasma NGAL levels cannot be translated directly to increased NGAL expression in adipocytes. Nonetheless, a recent study in 90 obese women showed that plasma NGAL levels were associated with visceral NGAL protein levels ($r=.43$, $p=.044$), while the latter were associated with visceral NGAL mRNA levels ($r=.59$, $p=.004$) (Auguet et al, 2010). The direct association between plasma levels and adipocyte mRNA, however, has not been reported. Thirdly, the comparison group was recruited from persons visiting the GP and especially obese persons do have a higher disease burden. This might have partly contributed to our finding of lower level of obesity in late-life depression. Fourthly, there is a small chance (one of 20) that we found some spurious findings (type one error) due to multiple comparisons. However, if one tests for the significance of an association using variables that are mutually correlated, the Bonferroni correction is even too conservative (Perneger, 1998). Therefore, we have not made the Bonferroni correction, but have chosen to present all individual statistics and p-values. Finally, we did not apply Computer Tomography at the level of the fourth lumbar vertebra as the gold standard for quantification of visceral fat (Weber-Haman et al, 2006).

Final conclusion and clinical implications

We conclude that population-based findings among older persons cannot be generalised to a clinical sample of depressed patients. Acknowledging the age-specific effects, we argue for further longitudinal studies specifically in depressed older persons. Such studies might be able to identify depressed subgroups with an unfavourable prognosis with respect to their physical health status. In these studies, the whole array of adipokines should be tested as well as the relative impact of the waist circumference in proportion to the general level of obesity as indexed by the body mass index.

References

Aalto M, Alho H, Halme JT et al. (2011) The Alcohol Use Disorders Identification Test (AUDIT) and its derivatives in screening for heavy drinking among the elderly. *International Journal of Geriatric Psychiatry;* 26:881-885.

Auguet T, Quintero Y, Terra X et al. (2011) Upregulation of Lipocalin 2 in adipose tissues of severely obese women: positive relationship with proinflammatory cytokines. *Obesity;* 19:2295-2300.

Alexander CM, Landsman PB, Teutsch SM et al. Third National Health and Nutrition Examination Survey (NHANES III); National Cholesterol Education Program (NCEP). (2003)NCEP-defined metabolic syndrome, diabetes, and prevalence of coronary heart disease among NHANES III participant sage 50 years and older. *Diabetes;* 52(5):1210-4.

Andrew MK, Rockwood K. (2007) Psychiatric illness in relation to frailty in community-dwelling elderly people without dementia: A report from the Canadian Study of Health and Aging. *Canadian Journal on Aging;* 26:33-38.

Arterburn D, Westbrook EO, Ludman EJ et al. (2012) Relationship between obesity, depression and disability in middle-aged women. *Obesity research & clinical practice;* 6:197-206.

Balu DT, Carlson GC, Talbot K et al. (2012) Akt1 deficiency in schizophrenia and impairment of hippocampal plasticity and function. *Hippocampus* 22:230-240.

Babor TFHB, Saunders JC, Monteiro JB et al. (2001) AUDIT - The alcohol use disorders identification test: guidelines for use in primary care, 2nd ed., Geneva, Switzerland, World Health Organisation.

Boer de A, Ter Horst AJ, Lorsit MM. (2013) Physiological and psychosocial age-related changes associated with reduced food intake in older persons. *Ageing Research Reviews;* 12(1):316-28.

Bremmer MA, Beekman AT, Deeg DJ et al. (2008) Inflammatory markers in late-life depression: results from a population-based study. *Journal of Affective Disorders;* 106(3):249-55.

Collard RM, Boter H, Schoevers RA et al. (2012) Prevalence of frailty in community-dwelling older persons: a systematic review. *Journal of the American Geriatrics Society;* 60(8):1487-92.

Collard RM, Comijs HC, Naarding P et al. (2013) Physical frailty: Vulnerability of patients suffering from late-life depression. *Aging Mental Health;* Sep 3 [Epub ahead of print].

Comijs, HC, van Marwijk HW, van der Mast RC et al. (2011) The Netherlands study of depression in older persons (NESDO); a prospective cohort study. *BMC Researc Notes;* 4:524.

Craig CL, Marshall AL, Sjostrom M et al. (2003) International physical activity questionnaire: 12-country reliability and validity. *Medicine and science in sports and exercise;* 35:1381-1395

Daly M. (2013) The relationship of C-Reactive Protein to obesity-related depressive symptoms: a longitudinal study. *Obesity;* 21:248-250.

Dantzer R, O'Connor JC, Freund GC et al. (2008) From inflammation to sickness and depression: when the immune system subjugates the brain. *Nature Reviews Neuroscience;* 9(1):46-56.

Deuschle M, Weber B, Colla M et al. (1998) Effects of major depression, aging and gender upon calculated diurnal free plasma cortisol concentrations: a re-evaluation study. *Stress;* 2(4):281-287.

Dixon JB, Dixon ME, O/Brien PE. (2003) Depression in association with severe obesity. *Archives*

Internal Medicine; 163:2058-2065.

Dong Q, Liu JJ, Zheng RZ et al. (2013) Obesity and depressie symptoms in the elderly: a survey in the rural area of Chizhou, Anhui provence. *International Journal of Geriatric Psychiatry;* 28:227-232.

Dowlati Y, Herrmann N, Swardfager W et al. (2010) A Meta-Analysis of Cytokines in Major Depression. *Biological Psychiatry;* 67:446-457.

Everson-Rose SA, Lewis RR, Karavolos K et al. (2009) Depressive symptoms and increased visceral fat in middle-aged women. *Psychosomatic Medicine;* 71:410-416.

Folstein M, Folstein S, McHugh P. (1975) "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research;* 12:189-198.

Fried LP, Tangen CM, Walston J et al. Cardiovascular Health Study Collaborative Research Group. (2001) Frailty in older adults: evidence for a phenotype. *The Journals of Gerontology Series A: Biological Sciences;* 56: M146-156.

Hegeman JM, Wardenaar KJ, Comijs HC et al. (2012) The subscale structure of the Inventory of Depressive Symptomatology Self Report (IDS-SR) in older persons. *Journal of Psychiatric Research; 46*:1383-1388.

Ho RCM, Niti M, Kua EH et al. (2008) Body mass index, waist circumference, waist-hip ratio an depressive symptoms in Chinese elderly: a population-based study. *International Journal of Geriatric Psychiatry;* 23:401-408.

Huang Y, Yang Z, Ye Z et al. (2012) Lipocalin-2, glucose metabolism and chronic low-grade systemic inflammation in Chinese people. *Cardiovascular Diabetology;* 11:11-18.

Ip JP, Nocon AL, Hofer MJ et al. (2011) Lipocalin 2 in the central nervous system host response to systemic lipopolysaccharide administration. *J Neuroinflammation;* 8:124.

Jin Y, Sui HJ, Dong Y et al. (2012) Atorvastatin enhances neurite outgrowth in cortical neurons in vitro via up-regulating the Akt/mTOR and Akt/GSK-3beta signaling pathways. *Acta Pharmacol Sin;* 33:861-872.

Karege F, Perroud N, Burkhardt S et al. (2011) Alterations in phosphatidylinositol 3-kinase activity and PTEN phosphatase in the prefrontal cortex of depressed suicide victims. *Neuropsychobiology;* 63:224-231.

Kessler RC, Birnbaum H, Bromet E et al. (2010) Age differences in major depression: results from the National Comorbidity Survey Replication (NCS-R). *Psychological Medicine;* 40:225-237.

Kriegsman DM, Penninx BW, van Eijk JT et al. (1996) Self-reports and general practitioner information on the presence of chronic diseases in community dwelling elderly. A study on the accuracy of patients' self-reports and on determinants of inaccuracy. *Journal of clinical epidemiology;* 49:1407-1417.

Luppino FS, de Wit LM, Bouvy PF et al. (2010) Overweight, obesity and depression. A systemic review and meta-analysis of longitudinal studies. *Archives General Psychiatry;* 67:220-229.

Marijnissen RM, Bus BA, Holewijn S et al. (2011) Depressive symptom clusters are differentially

associated with general and visceral obesity. *Journal of the American Geriatrics Society;* 59(1):67-72.

Marijnissen RM, Smits JEMP, Schoevers RA et al. (2013) Association between metabolic syndrome and depressive symptom profiles: sex-specific? *Journal of Affective Disorders,* 151(3):1138-1142.

Matsuzamwa Y, Funahashi T, Nakamura T. (2011) The concept of metabolic syndrome; contribution of visceral fat accumulation and its molecular mechanism. *Journal of Atheroscleris and Thrombosis;* 18:629-639.

Mathieu P, Poirier P, Pibarot P et al. (2009) Visceral Obesity: the link among inflammation, hypertension and cardiovascular disease. *Hypertension;* 53:577-584.

Milaneshi Y, Simonsick EM, Vogelzangs N et al. (2012) Leptin, abdominal obesity and onset of depression in older men and women. *Journal of Clinical Psychiatry;* 73(9):1205-1211.

Mucha M, Skrzypiec AE, Schiavon E et al. (2011) Lipocalin-2 controls neuronal excitability and anxiety by regulating dendritic spine formation and maturation. *Proc Natl Acad Sci;* 108:18436-18441.

Naudé PJW, Nyakas C, Eiden LE et al. (2012) Lipocalin 2: Novel component of proinflammatory signaling in Alzheimer's disease. *The FASEB Journal;* 26:2811.

Naudé PJW, Eisel ULM, Comijs HC et al. (2013) Neutrophil Gelatinase-Associated Lipocalin: A novel inflammatory marker associated with late-life depression. *J Psychosom Res;* 75(5):444-50.

Pasquali R. (2012) The hypothalamic-pituitary-adrenal axis and sex hormones in chronic stress and obesity: pathophysiological and clinical apects. *Annals of the New York Academy of Sciences;* 20-35.

Penninx BW, Beekman AT, Honig A et al. (2001) Depression and cardiac mortality: results from a community-based longitudinal study. *Archives General Psychiatry;* 58(3):221-227.

Penninx BWJH, Zitman FG. (2013)The impact of stress systems and lifestyle on dyslipidemia and obesity in anxiety and depression. *Psychoneuroendocrinology;* 38:209-218.

Perneger TV. (1998) What's wrong with Bonferroni adjustments. *British Medical Journal;* 316(7139):1236-8.

Roberts RE, Deleger S, Strawbridge WJ et al. (2003) Prospective association between obesity and depression: evidence from the Alameda County Study. *International Journal of Obesity* 27: 514-521.

Rush AJ, Gullion CM, Basco MR et al. (1996). The Inventory of Depressive Symptomatology (IDS): psychometric properties. *Psychological Medcine;* 26(3):477-486.

Sachs-Ericsson N, Burns AB, Gordon KH et al. (2007) Body mass index and depressive symptoms in older adults: The moderating roles of race, sex, and socioeconomic status. *Am J Geriatr Psychiatry;* 15:815–825.

Schwartz TL, NihalaniN, Virk S et al. (2004) Psychiatric medication-induced obesity: Treatment options. *Obesity Reviews;* 5:233–238.

Stunkard AJ, Faith MS, Allison KC. (2003) Depression and obesity. *Bioligal Psychiatry;* 54:330-337.

Taylor VH, Macqueen GM. The role of adipokines in understanding the associations between obesity and depression. (Epub 2010) *Journal of Obesity;* pil 748048. Doi: 10.1155/2010/748048.

Trujillo ME, Scherer PE. (2006) Adipose tissue-derived factors: impact on health and disease. *Endocrinve Reviews;* 27(7):762-078.

Van Reedt Dortland AKB, Vreeburg SA, Giltay EJ et al. (2013) Longitudinal relationship of depressive and anxiety symptoms with dyslipidemia and abdominal obesity. *Psychosomatic Medicine;* 75: 83-89.

Vogelzangs N, Kritchevsky SB, Beekman AT et al. (2008) Depressive symptoms and change in abdominal obesity in older persons. *Archives general psychiatry;* 65 (12):1386-1393.

Vogelzangs N, Beekman AT, Boelhouwer IG et al. (2011) Metabolic depression: a chronic depressive subtype? Findings from the InCHIANTI study of older persons. *Journal of Clinical Psychiatry;* 72(5):598-604.

Wang Y, Lam KSL, Kragen EW et al. (2007) Liipocalin-2 is an inflammatory marker closely associated with obesity, insulin resistance and hyperglycemia in humans. *Clinical Chemistry;* 53(1):34-41.

Weber-Hamann B, Werner M, Hentschel F et al. (2006) Metabolic changes in elderly patients with major depression: Evidence for increased accumulation of visceral fat at follow-up. *Psychoneuroendocrinology;* 31:347-354.

Wit de LM, van Straten A, van Herten M et al. (2009) Depression and body mass index, a u-shaped association. *BMC Public Health;* 1:9-14.

Wit de L, Luppino, F, van Straten A et al. (2010) Depression and obesity: a meta-analysis of community-based studies. *Psychiatry Research;* 30;178(2):230-5.

Wittchen HU, Robins LN, Cottler LB et al. (1991) Cross-cultural feasibility, reliability and sources of variance of the Composite International Diagnostic Interview (CIDI). The Multicentre WHO/ADAMHA Field Trials. *British Journal of Psychiatry;* 159:645-653, 658.

Wong SYS, Lueng JC, Leung PC et al. (2011) Depressive symptoms and change in abdominal obesity in the elderly: positive or negative association? *American Journal of Geriatric Psychiatry;* 19:730-742.

World Health Organization: Composite International Diagnostic Interview (1997) Version 2.1, Geneva, WHO.

World Health Organization (WHO) Collaborating Centre for Drug Statistics Methodology 2011. http://www.whocc.no/atc_ddd_index/. Accessed January 2012.

Zhao P & Stephens J. (2013) STAT1, NF-kB and ERKs play a role in the induction of lipocalin-2 expression in adipocitytes. *Molecular Metabolism;* 2:161-170.

Part two

Atherosclerosis and neuroticism

CHAPTER 5

Depressive symptom profiles are differentially associated with atherosclerosis

Published

Depressive symptom clusters are differentially associated with atherosclerotic disease

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Abstract

Background – Depression increases the risk of subsequent vascular events in both cardiac and non-cardiac patients. Atherosclerosis, the underlying process leading to vascular events, has been associated with depression. This association, however, may be confounded by the somatic-affective symptoms being a consequence of cardiovascular disease. While taking into account the differentiation between somatic-affective and cognitive-affective symptoms of depression, we examined the association between depression and atherosclerosis in a community-based sample.

Methods – In 1261 participants of the Nijmegen Biomedical Study (NBS), aged 50 through 70 and free of stroke and dementia, we measured the intima media thickness (IMT) of the carotid artery as a measure for atherosclerosis and we assessed depressive symptoms using the Beck Depression Inventory (BDI). Principal components analysis (PCA) of the BDI-items yielded two factors, representing a cognitive-affective and a somatic-affective symptom cluster. While correcting for confounders, we used separate multiple regression analyses to test the BDI sum score and both depression symptom clusters.

Results – We found a significant correlation between the BDI sum score and the IMT. Somatic-affective, but not cognitive-affective symptoms, were also associated with the IMT. When we stratified for coronary artery disease (CAD), the somatic-affective symptom cluster significantly correlated with depression both in patients with and patients without CAD.

Conclusions – The association between depressive symptoms and atherosclerosis is explained by the somatic-affective symptom cluster of depression. Subclinical vascular disease thus may inflate depressive symptom scores and may explain why treatment of depression in cardiac patients hardly affects vascular outcome.

Keywords

Depression, Intima Media Thickness (IMT), aged, elderly, cognitive-affective, somatic-affective, factor analysis, atherosclerosis

Introduction

Meta-analyses have shown that depressed, but otherwise healthy, individuals have an increased risk of developing coronary artery disease (CAD) (Van der Kooy et al, 2007), whereas depressed cardiac patients are at an increased risk of subsequent cardiovascular events (Carney et al, 1988; Barefoot et al, 1996; Wouts et al, 2008). Large randomized controlled trials aimed at improving cardiovascular prognosis by treatment of comorbid depression, however, did not affect vascular outcome and had only modest effects on depression (Glassman et al, 2002; Lesperance et al, 2007; van Melle et al, 2007).

Generalized atherosclerotic disease, the underlying process that contributes to vascular events, can be reliably measured by the intima media thickness (IMT) of the carotid artery (Bots et al, 1996) and has been associated consistently with a negative cardiovascular outcome (Bots et al, 1997). Epidemiological studies have shown up to a twofold increased risk for generalized atherosclerosis in depressed *versus* never depressed patients (Jones et al, 2003; Tiemeier et al, 2003; Tiemeier et al, 2004; Elovainio et al, 2005; Chen et al, 2006; Spitzer et al, 2008; Pizzi et al, 2008).

An important aspect in examining co-morbidity between depression and CAD is the definition of depression. According to the DSM-IV-TR, depressive disorder is a syndrome including both cognitive and somatic symptoms (de Jonge et al, 2006a). These symptoms are reflected in most self-report questionnaires measuring the severity of depression. This may result in inflated associations between CAD and depression. For example, symptoms of fatigue, sleep disturbances and loss of libido can be related to CAD, to depression or to both (Lindgren et al, 2008). Individual symptoms from both the cognitive and somatic symptom cluster have been associated with an increased risk of cardiovascular morbidity (Pedersen et al, 2007; Davidson et al, 2010; Doyle et al, 2010), although these results still remain to be confirmed and contradicting results have been found for fatigue and anhedonia (Davidson et al, 2010; Doyle et al, 2010). Of note, more consistent results are found on the symptom cluster level. In depressed cardiac patients, only the somatic-affective symptom cluster of depression was related to subsequent vascular events, but not the cognitive-affective symptom cluster (de Jonge et al, 2006; Martens et al, 2010).

This current study was conducted to examine the relationship between depressive symptom clusters and atherosclerosis in a community-based sample of people aged

between 50 and 70 years. We hypothesized that the association between depression and atherosclerosis would be driven primarily by the somatic-affective symptom cluster within the depressive syndrome and that this association would not be affected by the clinical vascular disease status, i.e the presence of coronary artery disease.

Methods

Sample

A total of 1517 subjects from the Nijmegen Biomedical Study were included. The Nijmegen Biomedical study is a population-based survey as described in detail elsewhere (Hoogendoorn et al, 2006). We invited participants, aged 50 through 70 years, to the hospital to participate in a detailed assessment of atherosclerotic disease, its risk factors and consequences (Holewijn et al, 2009). Exclusion criteria were a diagnosis of dementia or a history of stroke, as these conditions might directly affect the neurobiological brain circuits involved in depression (Alexopoulos, 2005). The Medical Ethics Committee of the Radboud University Nijmegen Medical Centre approved the study protocol (which is in accordance with the Declaration of Helsinki), and all participants provided written informed consent.

Variables of interest

Carotid intima media thickness (IMT) - Carotid IMT was determined using semi-automatic edge-detection software (M'AthSTD version 2.0,Metris, Argenteuil, France). IMT was defined as the mean IMT of four measured segments of the distal common carotid artery: far wall left, near wall left, far wall right and near wall right. Longitudinal images of the most distal 10 mm of both the far wall and the near wall of both common carotid arteries were obtained in the optimal projection (anterolateral, lateral or posterolateral). IMT was measured in an area free of plaque, which was defined as an area with an IMT ≥ 1.5 times the surrounding IMT. All measurements were carried out in end-diastole using the R-wave of a simultaneously recorded ECG as a reference frame. From each frame the mean IMT was calculated over at least 7.5 mm of the above mentioned 10 mm segment (yielding a quality index of at least 75%). The outcome variable was defined as the mean IMT of the near and far wall of both common carotid arteries. IMT measurements were performed after an overnight fast or in the afternoon 6 hours after a standardized breakfast. Participants were asked to abstain from caffeinated products for at least 12 hours and they were asked not to smoke for 12 hours before the visit. After standardizing the measurement conditions, there were no significant differences between the measurements performed in the morning and those performed in the afternoon (details available in Ter Avest et al, 2005). Participants

Table 1 Factor loadings of depressive symptom dimensions and relation to Beck Depression Inventory items and previous dimensional constructs.

Items of the Beck Depression Inventory	Original Beck & Steer dimensional structure	Dimensional structure De Jonge et al (2006)			Dimensional structure present study[a]	
		Cognitive - Affective factor	Somatic - Affective factor	Appetitive factor	Cognitive - Affective factor	Somatic - Affective factor
Sadness	Cognitive	0.45	0.64		0.43	0.27
Pessimism	Cognitive	0.58	0.56		0.56	0.18
Sense of failure	Cognitive	0.66			0.68	-0.02
Dissatisfaction	Cognitive	0.49	0.69		0.35	0.46
Guilt	Cognitive	0.70			0.61	-0.02
Punishment	Cognitive	0.59			0.50	-0.01
Self-dislike	Cognitive	0.72			0.68	-0.05
Self-accusations	Cognitive	0.71			0.71	-0.10
Suicidal ideas	Cognitive	0.49			0.65	-0.05
Crying	Cognitive		0.52		0.24	0.34
Irritability	Cognitive		0.45		0.09	0.42
Social withdrawal	Cognitive	0.51	0.42		0.15	0.36
Indecisiveness	Cognitive	0.40	0.68		0.33	0.40
Body image change	Somatic	0.57			0.35	0.16
Work difficulty	Somatic		0.69		0.11	0.63
Insomnia	Somatic		0.55		0.14	0.42
Fatigability	Somatic		0.58		-0.13	0.64
Loss of appetite	Somatic		0.42	0.65	-0.14	0.55
Weight loss	Somatic			0.66	-0.07	0.26
Somatic preoccupation	Somatic		0.67		0.07	0.46
Loss of libido	Somatic		0.50		0.01	0.50

[a] Rotate component. Extraction method: Principal Component Analysis. Rotation method: Oblimin with Kaiser Normalization.

were measured in supine position in a room with controlled temperature (23 - 24º C). The equipment used was a 7.5 MHz transducer of an AU5 ultrasound system (Esaote Biomedical, Genova Italy), connected to a computer with a data acquisition board. All measurements were highly standardized and performed by well-trained and certified sonographers. The reproducibility of our IMT-measurements was investigated and reported previously (Holewijn et al, 2009).

Depressive symptoms - Depressive symptoms were measured by the Beck Depression Inventory (BDI; Beck & Steer, 1984). The BDI is a 21-item self-report questionnaire with excellent psychometric characteristics. Each item is rated on a 0 to 3 scale, with 0 representing 'absence' and 1-3 representing increasing levels of severity of the symptom. The BDI yields a total score ranging from 0 to 63. Information on history of depression was collected on the basis of an interview.

Principal components analysis (PCA) with oblimin rotation was conducted on the 21 individual BDI items to obtain fewer factors/components while retaining the original item information. We selected PCA rather than factor analysis for 2 reasons: 1) its ultimate goal is to reduce data to components useful for other purposes (in this case to examine associations of IMT and aggregate types of depressive symptoms rather than individual depressive symptoms), as opposed to the primary goal of factor analysis, which is to reveal underlying variables that cause manifest variables to co-vary; and 2) its superior ability to remedy multicollinearity among factors. Factor scores were calculated on unstandardized item factor loadings and transformed into standardized z scores (using the Anderson-Rubin method) to increase their interpretability (Costello and Osborne, 2009).

Three criteria were used to select the best overall solution, namely factors with eigen-values greater than 1, the scree plot of eigenvalues and the number of complex items. Although 5 factors emerged with an eigen-value greater than 1, combination of the above-mentioned criteria indicated that a two-factor solution was the optimal solution. The PCA specified to extract only two factors revealed a solution comparable to the traditional two-factor structure of the BDI, i.e. cognitive-affective *versus* somatic-affective symptoms, see also Table 1 for comparison. (KMO-measure of sampling adequacy: .898; Bartlett's test of sphericity: chi-square=5074; df=210;p<.001; explained variance factor 1: 24.3%; factor 2: 7.6%).

Covariates

Variables that were examined as potential confounders were age, sex, metabolic

syndrome, smoking status, physical activity, alcohol use, cardiovascular medication and cardiovascular disease status. Individual components of the metabolic syndrome were measured; mean arterial pressure was measured using an oscillometric sphygmanometer (Criticon model no. 1846, Criticon Inc., Tampa, USA). Waist circumference was measured at the level of the umbilicus. Triglycerides and glucose concentrations were determined using commercially available enzymatic reagents (AEROSET® System, Abbott, Chicago Illinois). Metabolic syndrome (MS) was defined according to the International Diabetes Federation (IDF, 2009).
Smoking status, alcohol use, physical activity and cardiovascular disease status were assessed during a short interview. Smoking behaviour was categorised as current, former or never. Physical activity was based on the number of exercise sessions per week of more than 30 minutes moderate to vigorous activity (Stampfer et al, 2000). Because of a skewed distribution (that could not be normalized by transformation), a median split was used (0 or 1 *versus* 2 or more exercise moments/week).
Coronary artery disease (CAD) was assessed by a trained interviewer and defined as a history of treated angina pectoris, myocardial infarction, a history of percutaneous transluminal coronary angioplasty or coronary artery bypass grafting (Kriegsman et al, 1996). Alcohol intake was dichotomized into severe use (>21 for males and >14 for females) and non-severe use.

Medication use was defined by the use of at least half of the defined daily dose and based on brought-alone medication containers. Eight different classes of medication were selected based on their potential influence on atherosclerotic disease and/or its association with depression and entered as dichotomies (yes/no). These classes were antidepressants (ATC N06AXXX), statins (ATC C10AXXX), ACE-inhibitors (ATC C09AXXX), Angiotensin-II-antagonists (C09CATC), Ca+-channelblockers (C08CXXX, C08DXXX, C08EXXX), β-blockers (ATC C07.AXXX), diuretics (C03XXXX), analgesics (N02BAXX).

Statistical methods
In case of one or two missing items on the BDI we imputed the series mean, which is a reliably procedure in case of less than 10% missing values (Shrive et al, 2006). Only 71 subjects had one or two missing items (percentage missing: 86 of 26.481 items ≈ 0.3%). Subjects with more than two missing items were excluded. As BDI scores showed a skewed distribution we used the log-transformed BDI scores in all analyses.

IMT values were normally distributed in our population. To evaluate associations of the IMT with BDI scores, we used multiple linear regression analysis with the IMT as the dependent variable. Multiple regression models were conducted, first only corrected

for age and sex (block 1) and subsequently also the individual measurements that make up for the metabolic syndrome [mean arterial blood pressure (mmHg), triglycerides (mmol/L), High density lipoprotein (mmol/L), glucose (mmol/L) and waist circumference (cm)] (block 2) and lifestyle factors such as smoking status (former/current/never), alcohol use (dichotomized), physical activity (dichotomized), history of depressive disorder (dichotomized) and prevalent coronary artery disease (block 3), finally also medication use (antidepressants (yes/no), statins (yes/no), ACE-inhibitors (yes/no), Angiotensin-II-antagonists (yes/no), Ca+-channelblockers (yes/no) and β-blockers (yes/no), diuretics (yes/no), (analgesics yes/no), other medication (yes/no)) was entered (block 4).
In a second multiple regression model we replaced the BDI sum score by the factor scores (somatic-affective or cognitive-affective symptoms) as a measure for depression. In order to exclude the possibility that the main effects are caused by CAD as a stressful vascular event, we subsequently stratified the analyses by the presence of CAD by adding an interaction term between BDI sumscore and CAD. All statistical analyses were carried out using SPSS version 16.0 (SPSS Inc., USA) All analyses were tested two-sided; p-values less than .05 were considered statistically significant.

Results

Of the 1517 subjects who consented to participation in the study of non-invasive measurements of atherosclerosis, 29 subjects were excluded because of a history of stroke. None of the participants was diagnosed with dementia. In addition, 227 (15.3%) subjects were excluded because of missing data caused by: not responding to the postal questionnaire containing the BDI (n=181); having three or more missing items on the BDI (n=36); or violating the rules for a reliable measurement of atherosclerotic disease or its risk factors (i.e. having smoked before coming to the hospital, n=3; not obeying the pre-test fasting protocol, n=2; and not stopping their lipid lowering medication, n=5)

Subjects with missing data (227/1488, 15.3%) differed from subjects included (n=1261) with respect to mean age (62.1 v 60.0 years respectively; $t_{1486} = 2.49$; $p = .013$), severe alcohol use (6% v. 12% respectively; $t_{1486} = -2.70$; $p = .007$), physical activity (30% v. 37%; $t_{1486} = -2.13$; $p = .033$) and current smoking (25% v. 17%; $t_{1486} = 2.82$; $p = .005$). The IMT, however, did not differ between these groups (respectively 0.86 v. 0.84mm $t_{1456} = 1.53$; $p = .13$).

The final study population consisted of 1261 persons with a mean age of 61.0 years

Table 2 Differences between CAD patients and healthy subjects.

	CAD (n = 82)	No CAD (n = 1179)
IMT, mm (SD)	0.88 (0.23)	0.84 (0.11)
BDI sum score, median (IQR) *	4 (2-8)	6 (4-11)
Sociodemographics		
% female (n) *	30.5 (25)	52.3 (617)
Age in years, mean (SD) *	60.9 (5.8)	62.8 (6.1)
Health indicators		
% currently smoking (n)	22.0 (18)	16.9 (199)
% formerly smoking (n)	56.0 (46)	49.4 (583)
% severe alcohol users (n)	12.2 (10)	11.7 (138)
% with 2 or more sportmoments a week (n)	30.5 (25)	37.3 (440)
% with metabolic syndrome (n) *	63.4 (52)	30.8 (363)
Mean arterial pressure, mmHG (SD)	111.0 (13.7)	111.8 (12.7)
High density lipoprotein, mmol/L (SD) *	1.19 (0.34)	1.43 (0.37)
Glucose, mmol/L (SD) *	5.82 (1.77)	5.18 (0.83)
Waist circumference cm, (SD) *	98.6 (13.0)	94.0 (12.2)
Triglycerides, mmol/L (SD) *	2.10 (1.28)	1.40 (0.75)
% with history of depression (n)	13.2 (19)	19.2 (226)
Medication		
% using antidepressants (n)	2.4 (2)	3.9 (46)
% using ACE-inhibitor (n) *	29.3 (24)	5.9 (70)
% using betablockers (n) *	69.5 (57)	12.2 (144)
% using Ca^{+}-antagonists (n)	18.3 (15)	2.5 (30)
% using angiotensin-II-antagonists (n)	8.5 (7)	3.3 (39)
% using statins (n)	74.4 (61)	10.2 (120)
% using diuretics (n)	14.9 (12)	10.9 (129)
% using analgetics (n)	8.5 (7)	7.2 (85)

Abbreviations: CAD, coronary artery disease; SD, standard deviation; BDI, Beck Depression Inventory; IQR, interquartile range; ACE, Angiotensin converting enzyme
* Significant difference at a $p < .01$ level.

(SD=5.9 years) and 642 (51%) were females. The median score on the BDI was 4 (interquartile range 2-8; range 0 – 30) and the mean IMT was 0.84 mm (SD=0.12 mm, range 0.57 - 2.54 mm). Table 2 presents the characteristics of all participants stratified by CAD status.

Table 3 Association of depressive symptoms with intima media thickness (IMT), corrected for different sets of covariates.

		Intima Media Thickness								
Variable(s) of interest	Included co-variates	All participants			CAD in history			No CAD in history		
		B	β	*P* value	B	β	*P* value	B	β	*P* value
Model 1										
BDI sumscore	Demographics[a]	0.024	.07	.01	0.161	.21	.04	0.014	.05	.09
	+ Metabolic syndrome	0.017	.05	.05	0.140	.19	.10	0.009	.03	.28
	components[b]									
	+ Lifestyle and disease[c]	0.018	.05	.05	0.165	.22	.07	0.008	.03	.33
	+ Medication[d]	0.019	.05	.04	0.149	.20	.11	0.010	.03	.23
Model 2										
Cognitive BDI score	Demographics[a]	-0.008	-.06	.02	-0.021	-.08	.43	-0.006	-.05	.06
	+ Metabolic syndrome	-0.007	-.06	.03	-0.030	-.12	.27	-0.006	-.05	.07
	components[b]									
	+ Lifestyle and disease[c]	-0.008	-.06	.02	-0.028	-.11	.33	-0.007	-.06	.03
	+ Medication[d]	-0.008	-.06	.02	-0.013	-.05	.65	-0.007	-.06	.03
Somatic BDI score	Demographics[a]	0.015	.13	<.001	0.076	.36	.001	0.009	.08	.004
	+ Metabolic syndrome	0.012	.10	<.001	0.075	.35	.003	0.006	.06	.04
	components[b]									
	+ Lifestyle and disease[c]	0.013	.10	<.001	0.081	.38	.003	0.007	.06	.04
	+ Medication[d]	0.013	.11	<.001	0.075	.35	.01	0.007	.07	.03

[a] Linear regression analysis adjusted for sex and age.

[b] Previous model plus glucose, mean arterial pressure, waist circumference, HDL and triglycerides. Similar results were obtained when metabolic syndrome was entered as a dichotomous variable (yes/no) rather than it's separate components.

[c] Previous model plus smoking (current/former/never), alcohol consumption (yes/no), physical activity (yes/no), history of depression (yes/no), in case of all participant also prevalent cardiovascular disease (yes/no)

[d] Previous model plus medication antidepressants (yes/no), statins (yes/no), Ca+-channelblockers (yes/no), angiotensine-II-antagonists (yes/no), Betablockers (yes/no), ACE-inhibitors (yes/no), diuretics (yes/no), analgetics (yes/no), other cardiovascular medication (yes/no)

Abbreviations: CAD, coronary artery disease; BDI, Beck Depression Inventory.

As shown in Table 3, we found a significant correlation between the BDI sum score and the IMT. After we divided the depressive symptoms into a cognitive-affective symptoms cluster and a somatic-affective symptom cluster, the IMT proved to be negatively associated with the former ($\beta = -.06$; $p = .02$) and positively with the latter ($\beta = .11$; $p < .001$).

To examine whether the relationship between IMT and depressive symptoms was explained primarily by CAD, we added an interaction term of CAD and depressive symptoms. While controlling for the effects of other covariates, this interaction term was significant in model 1 (β=0.22, p=.011; model statistics: R^2=.24; $F_{26,1234}$=18.46, p<.001). However, in model 2, only the interaction between the somatic-affective symptom cluster and CAD remained significant (β=0.15, p<.001; model statistics: R^2=.25; $F_{28,1232}$=18.42, p<.001), but not the interaction between the cognitive-affective symptom cluster and CAD (β= -.023, p=.38). The somatic-affective symptom cluster was significantly associated with the IMT in both patients with and without CAD, whereas the cognitive-affective symptom cluster negatively associated with IMT in the group without CAD.

Discussion

Main findings

We show that the positive association between depressive symptoms and subclinical atherosclerosis, as measured by IMT, is driven primarily by the somatic-affective symptom cluster of depression. Furthermore, as the association was present in patients with and without coronary artery disease (CAD), the relationship seems specific for atherosclerotic disease independent of vascular events, such as a stressful life-event.

Relationship between depressive symptoms and IMT

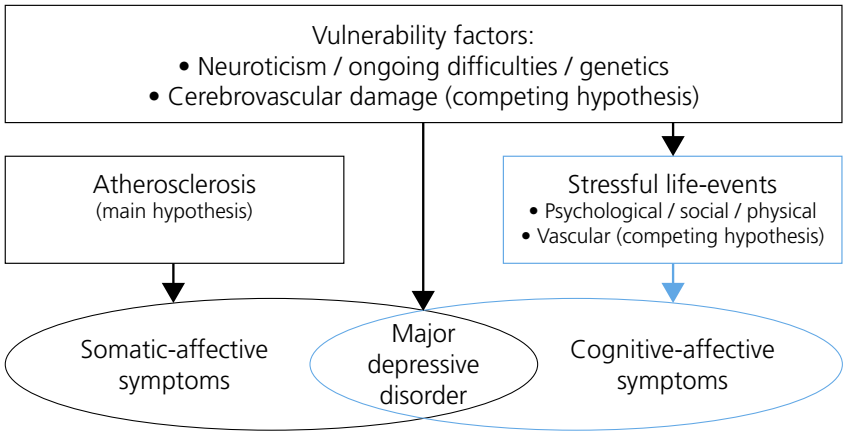
Previous studies have also reported a positive relationship between depressive symptoms and IMT (Jones et al, 2003; Tiemeier et al, 2004; Chen et al, 2006), although negative findings have been reported as well (Jones et al, 2003; Spitzer et al, 2008). As our effect-size was relatively small, these negative results can be explained by low patient numbers (Scarisbrick et al, 1993; Spitzer et al, 2008), but also by a lower age band of the population, resulting in significantly less severe atherosclerotic disease (Jones et al, 2003).

Different hypotheses have been postulated to explain the direction of association between depressive symptoms and atherosclerosis, including life-style factors, such as increased smoking and decreased physical activity in depressed patients and

pathophysiological disturbances associated with depression, such as hypercortisolaemia, low-grade inflammation, and autonomic arousal (Raison et al, 2006; Vreeburg et al, 2009; Carney and Freedland, 2009a). These mechanisms all have a final common pathway by promoting atherosclerotic disease. Two studies have identified a common genetic pathway for CAD and depression (Scherrer et al, 2003; Kendler et al, 2009).
However, cytokines have been shown to cause depressive symptoms by acting on the hypothalamus (Nijm et al, 2007). As atherosclerotic disease is currently regarded as a low-grade inflammatory process (Schuett et al, 2009), depression may thus be an epiphenomenon. Which of these mechanisms prevail may be determined by longitudinal studies with a vascular endpoint that include measures of depression in addition to measures of subclinical atherosclerosis such as IMT and inflammatory markers. To date, such studies are lacking.

Depressive symptom clusters and IMT
We have shown that the somatic symptoms, but not the cognitive symptoms, of depression contribute to the positive relationship between depression and the IMT. This finding suggests that depression might be an epiphenomenon of atherosclerotic disease: symptoms originating from subclinical atherosclerotic disease inflate the depressive symptom score resulting in too broad a definition of depression (see Figure 1). In other words, subjects with symptoms originating from atherosclerotic disease will score higher on the somatic-affective symptoms of the BDI, in which case only a small additional score

Figure 1 Chapter hypothesis.



on cognitive items is needed to meet the current definition of clinical depression. This hypothesis is supported by particular studies that have demonstrated that in particular somatic-affective, but not cognitive-affective symptoms of depression, predict cardiovascular morbidity and mortality (de Jonge et al, 2006; Linke et al, 2009). Furthermore, cluster analyses of symptoms of cardiovascular disease in elderly patients with ischemic heart disease yielded a cluster with patients particularly suffering from fatigue and sleep disturbances and as expected, the highest depressive symptom scores were found in this patient cluster (Lindgren et al, 2008).

The inverse association between IMT and the cognitive cluster seems puzzling at a first glance. In our opinion, it is most probably explained by an artifact due to a combination of low scores and negative factor loadings on cognitive items. Moreover, previous research has shown that single cognitive symptoms are associated with an increased risk for cardiovascular morbidity (Pedersen et al, 2007; Davidson et al, 2010) and no studies have shown a decreased risk for cardiovascular disease in subjects with high cognitive scores (de Jonge et al, 2011).

Of note, within a group of patients suffering from depression, higher IMT values were associated with a later age of onset (Smith et al, 2009). The effect of atherosclerosis on the development of late-onset depression was, in that study, to cerebrovascular damage, whereas it may also be explained by overlapping symptoms between atherosclerosis and (somatic-affective symptoms of) depression.

The association between the somatic-affective factor and IMT is further extended by the fact that we also found a positive association in subjects without a history of CAD, although it was significantly weaker than in subjects with CAD. Two explanations can be put forward. First, CAD may lead to a cardiotoxic process accompanied by high depressive symptoms scores (de Jonge et al, 2009). As this process is thought to be time-limited and the majority of our population suffers from chronic CAD, this is only a partial explanation. Second, the (very) small IMT values in non-CAD participants hardly lead to (somatic) symptoms. This explanation, however, suggests a non-linear relationship between increasing atherosclerosis and depressive symptoms (which is also indicated by the significant interaction term in our analyses). Nevertheless, the significant association in the group without CAD implies that the association between depression and coronary artery disease is not only driven by psychological stress associated with a life-threatening event or by an acute biological process associated with a myocardial infarction. Because of this low level of somatic-affective symptoms, and due to smaller patient numbers, the overall BDI sum score was not related to the

IMT anymore. This has also been reported in a study of middle-aged women with low IMT values (Jones et al, 2003).

Methodological considerations

The strengths of the present paper are the large sample size and reliable measures of depressive symptom clusters and subclinical atherosclerotic disease in middle-aged and older people at risk of cerebrovascular disease but prior to clinical stroke. For proper interpretation of the results some limitations have to be addressed. First, because vascular depression is known to have a specific somatic-affective symptom profile (Naarding et al, 2007) this type of depression might influence our findings. For this reason we excluded all evident cases of cerebrovascular disease by excluding subjects with a history of stroke (Krishnan et al, 2004; Steffens et al, 2004). Nevertheless, many researchers consider magnetic resonance imaging (MRI) of the cerebrum as the gold standard to identify vascular depression. Second, the cross-sectional design of this study does not allow our results to be interpreted causally. To date, no prospective studies are available relating depressive symptom clusters to subclinical vascular disease. Third, being a population sample, bias towards the most healthy people may have occurred, resulting in less (advanced) atherosclerosis and depressive symptoms. This may have resulted in less overall variance of the atherosclerosis and depression measures and also lowered the explained variance of the factors found.

Final conclusion and clinical implications

In addition to replicating a significant association between depressive symptoms and subclinical atherosclerotic disease, we are the first to show that this correlation could be explained by the somatic-affective symptom cluster within the depression symptomatology. This has major conceptual and clinical implications. From a conceptual point of view, subclinical atherosclerotic disease may inflate depressive symptom scores, possibly with large effects in CAD patients. This could argue for adaptations of the criteria for depressive disorder in patients with atherosclerosis with less emphasis on somatic-affective symptoms parallel to the degree of atherosclerotic disease. From a clinical point of view, these results may suggest misdiagnosis of depression in some cardiac patients due to the presence of somatic-affective symptoms that reflect severity of atherosclerotic disease, but are not part of a formal depressive syndrome. This hypothesis is supported by previous findings showing a worse cardiac outcome in CAD patients with treatment resistant depression only (de Jonge et al, 2006b; Carney and Freedland, 2009b), as those somatic-affective symptoms due to atherosclerosis may not be affected by antidepressants, but are related to cardiac outcome.

References

Alexopoulos GS. (2005) Depression in the elderly. *Lancet*; 365:1961-1970.

Barefoot JC, Helms M, Mark DB et al. (1996) Depression and long-term mortality risk in patients with coronary artery disease. *American Journal of Cardiology;* 78:613-617.

Beck AT & Steer RA. (1984) Internal consistencies of the original and revised Beck Depression Inventory. *Journal of Clinincal Psychology;* 40:1365-1367.

Bots ML, Hoes AW, Koudstaal PJ et al. (1997) Common carotid intima-media thickness and risk of stroke and myocardial infarction: the Rotterdam Study. *Circulation;* 96:1432-1437.

Bots ML, Hofman A, de Jong PT et al. (1996) Common carotid intima-media thickness as an indicator of atherosclerosis at other sites of the carotid artery. The Rotterdam Study. *Annals of Epidemiology;* 6:147-153.

Carney RM & Freedland KE (2009a) Depression and heart rate variability in patients with coronary heart disease. *Cleveland Clinical Journal of Medicine;* 76 Suppl 2:S13-S17.

Carney RM & Freedland KE (2009b) Treatment-resistant depression and mortality after acute coronary syndrome. *American Journal of Psychiatry;* 166:410-417.

Carney RM, Rich MW, Freedland KE et al. (1988) Major depressive disorder predicts cardiac events in patients with coronary artery disease. *Psychosomatic Medicine;* 50:627-633.

Chen CS, Chen CC, Kuo, YT et al. (2006) Carotid intima-media thickness in late-onset major depressive disorder. *International Journal of Geriatric Psychiatry;* 21:36-42.

Costello AB & Osborne JW (2009) Best Practices in Exploratory Factor Analysis: FourRecommendations for Getting the Most From Your Analysis. *Practical assesment, research and evaluation;* 10:1-9.

Davidson KW, Burg MM, Kronish IM et al. (2010) Association of anhedonia with recurrent major adverse cardiac events and mortality 1 year after acute coronary syndrome. *Archives of General Psychiatry; 67*:480-488.

de Jonge P, Ormel J, van den Brink RH et al. (2006a) Symptom dimensions of depression following myocardial infarction and their relationship with somatic health status and cardiovascular prognosis. *American Journal of Psychiatry;* 163:138-144.

de Jonge P, van den Brink RH, Spijkerman TA et al. (2006b) Only incident depressive episodes after myocardial infarction are associated with new cardiovascular events. *Journal of American College of Cardiology;* 48:2204-2208.

de Jonge P, Ormel J, van den Brink RH et al. (2006) Symptom dimensions of depression following myocardial infarction and their relationship with somatic health status and cardiovascular prognosis. *American Journal of Psychiatry;* 163:138-144.

de Jonge P. (2009). The importance of incident depression in myocardial infarction patients. *Biological Psychiatry;* 65:e7-e8.

Doyle F, Conroy R, McGee H et al. (2010) Depressive symptoms in persons with acute coronary syndrome: specific symptom scales and prognosis. *Journal of Psychosomatic Research;* 68:121-130.

Elovainio M, Keltikangas-Jarvinen L, Kivimaki M et al. (2005) Depressive symptoms and carotid artery intima-media thickness in young adults: the Cardiovascular Risk in Young Finns Study. *Psychosomatic Medicine;* 67:561-567.

Glassman AH, O'Connor CM, Califf RM et al. (2002) Sertraline treatment of major depression in patients with acute MI or unstable angina. *JAMA;* 288:701-709.

Holewijn, S., den Heijer M, Swinkels DW et al. (2009) Brachial artery diameter is related to cardiovascular risk factors and intima-media thickness. *European Journal of Clinical Investigation;* 39:554-560.

Hoogendoorn EH, Hermus AR, de Vegt F et al. (2006) Thyroid function and prevalence of anti-thyroperoxidase antibodies in a population with borderline sufficient iodine intake: influences of age and sex. *Clinical Chemistry;* 52:104-111.

IDF. (2009).The IDF consensus worldwide definition of the metabolic syndrome http://www.idf.org/webdata/docs/IDF_Meta_def_final.pdf

Jones DJ, Bromberger JT, Sutton-Tyrrell K et al. (2003) Lifetime history of depression and carotid atherosclerosis in middle-aged women. *Archives of General Psychiatry;* 60:153-160.

Kendler KS, Gardner CO, Fiske A et al. (2009) Major depression and coronary artery disease in the Swedish twin registry: phenotypic, genetic, and environmental sources of comorbidity. *Archives of General Psychiatry;* 66:857-863.

Kriegsman DMW, Penninx BWJH, van Eijk JThM et al. (1996) Self-Reports and General Practitioner Information on the Presence of Chronic Diseases in Community Dwelling elderly. *J. Clin. Epidemiol;* 49:1407-1417.

Krishnan KR, Taylor WD, Mc Quoid DR et al. (2004) Clinical characteristics of magnetic resonance imaging-defined subcortical ischemic depression. *Biological Psychiatry;* 55:390-397.

Lesperance F, Frasure-Smith N, Koszycki D et al. (2007) Effects of citalopram and interpersonal psychotherapy on depression in patients with coronary artery disease: the Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE) trial. *JAMA;* 297:367-379.

Lindgren TG, Fukuoka Y, Rankin SH et al. (2008) Cluster analysis of elderly cardiac patients' prehospital symptomatology. *Nursing Research;* 57:14-23.

Linke SE, Rutledge T, Johnson BD et al. (2009) Depressive symptom dimensions and cardiovascular prognosis among women with suspected myocardial ischemia: A report from the National Heart, Lung, and Blood Institute-sponsored Women's Ischemia Syndrome Evaluation. *Archives of General Psychiatry;* 66:499-507.

Martens EJ, Hoen PW, Mittelhaeuser M et al. (2010) Symptom dimensions of post-myocardial infarction depression, disease severity and cardiac prognosis. *Psych Medicine;* 40:807-814.

Naarding P, Tiemeier H, Breteler MM et al. (2007). Clinically defined vascular depression in the general population. *Psych Medicine;* 37:383-392.

Nijm J, Kristenson M, Olsson AG et al. (2007) Impaired cortisol response to acute stressors in

patients with coronary disease. Implications for inflammatory activity. *Journal of Internal Medicine;* 262:375-384.

Pedersen SS, Denollet J, Daemen J et al. (2007) Fatigue, depressive symptoms, and hopelessness as predictors of adverse clinical events following percutaneous coronary intervention with paclitaxel-eluting stents. *Journal Psychosomatic Research;* 62L:455-461.

Pizzi C, Manzoli L, Mancini S et al. (2008) Analysis of potential predictors of depression among coronary heart disease risk factors including heart rate variability, markers of inflammation, and endothelial function. *European Heart Journal;* 29:1110-1117.

Raison CL, Capuron L & Miller AH. (2006) Cytokines sing the blues: inflammation and the pathogenesis of depression. *Trends in Immunology*; 27:24-31.

Scarisbrick IA, Jones EG & Isackson PJ (1993) Coexpression of mRNAs for NGF, BDNF, and NT-3 in the cardiovascular system of the pre- and postnatal rat. *Journal of Neuroscience;* 13:875-893.

Scherrer JF, Xian H, Bucholz KK et al. (2003) A twin study of depression symptoms, hypertension, and heart disease in middle-aged men. *Psychosomatic Medicine;* 65:548-557.

Schuett H, Luchtefeld M, Grothusen C, et al. (2009) How much is too much? Interleukin-6 and its signalling in atherosclerosis. *Thrombosis and Haemostasis;* 102:215-222.

Smith PJ, Blumenthal JA, Babyak MA et al. (2009) Intima-media thickness and age of first depressive episode. *Biological Psychology;* 80:361-364.

Spitzer C, Volzke H, Barnow S, Krohn U et al. (2008) Association between depression and subclinical carotid atherosclerosis in patients with Type 1 diabetes. *Diabetic Medicine;* 25:349-354.

Stampfer MJ, Hu FB, Manson JE et al. (2000) Primary prevention of coronary heart disease in women through diet and lifestyle. *New England Journal of Med;* 343:16-22.

Steffens DC. (2004) Establishing diagnostic criteria for vascular depression. *Journal of Neurological Science;* 226:59-62.

Ter Avest E, Holewijn S, Stalenhoef AF et al. (2005) Variation in non-invasive measurements of vascular function in healthy volunteers during daytime. *Clinical Science (Lond) ;* 108:425-431.

Tiemeier H, Breteler MM, van Popele NM et al. (2003) Late-life depression is associated with arterial stiffness: a population-based study. *Journal of American Geriatric Society*; 51:1105-1110.

Tiemeier H, van Dijck DW, Hofman A et al. (2004) Relationship between atherosclerosis and late-life depression: the Rotterdam Study. *Archives of General Psychiatry;* 61:369-376.

Van der Kooy K, van Hout H, Marwijk H et al. (2007) Depression and the risk for cardiovascular diseases: systematic review and meta analysis. *International Journal of Geriatric Psychiatry;* 22:613-626.

van Melle JP, de Jonge P, Honig A et al. (2007) Effects of antidepressant treatment following myocardial infarction. *British Journal of Psychiatry;* 190:460-466.

Vreeburg SA, Hoogendijk WJ, van Pelt J et al. (2009) Major depressive disorder and hypothalamic-pituitary-adrenal axis activity: results from a large cohort study. *Archives of General Psychiatry;* 66:617-626.

Wouts L, Oude Voshaar RC, Bremmer MA et al. (2008) Cardiac disease, depressive symptoms, and incident stroke in an elderly population. *Archives of General Psychiatry;* 65:596-602.

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Atherosclerosis decreases the impact of neuroticism in late-life depression: hypothesis of vascular apathy

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Abstract

Background – Neuroticism and cardiovascular disease are vulnerability factors in late-life depression, but have hardly been examined in relation to each other. The objective of the study was to examine the interplay between subclinical atherosclerotic disease and neuroticism in explaining variance in late-life depressive symptoms.
Methods – This study was part of the Nijmegen Biomedical Study (NBS), a population based survey and included 1517 participants aged 50 through 70 years. Depressive symptoms were measured by the Beck Depression Inventory (BDI). Principal components analysis of the BDI-items yielded two factors, representing a cognitive-affective symptom cluster and a somatic-affective symptom cluster. Atherosclerotic disease was measured by the Intima Media Thickness of the carotid arteries(IMT) and neuroticism by the revised Eysenck Personality Questionnaire (EPQ-RSS).
Results – Multiple linear regression analyses using different measures of depressive symptoms as the dependent variable showed that neuroticism was strongly and significantly associated with the sum score of the BDI as well as with the two depressive symptom clusters. IMT, however, was only significantly associated with the somatic-affective symptom cluster, but not with the cognitive-affective symptom cluster. Interestingly, we found a significant negative interaction between neuroticism and IMT in explaining the severity of the cognitive-affective symptom cluster, but not with respect to the somatic-affective symptom cluster.
Conclusions – The negative interaction between neuroticism and atherosclerosis indicates that neuroticism is less strongly associated with cognitive-depressive symptoms in the presence of more severe atherosclerosis. This may be explained by apathy due to cerebrovascular disease and fits with a hypothesis of vascular apathy.

Keywords

Atherosclerosis, neuroticism, late-life depression, apathy, elderly

Introduction

Clinically relevant depressive symptoms are highly prevalent in later life, affecting 13.5% of elderly people in the community, with 1.8% meeting the criteria for major depressive disorder and 9.8% for minor depression. (Beekman et al, 1999). The stress-vulnerability model is a widely used model to explain depressive symptoms. This models states that stressors may lead to depression, especially in the presence of a long-standing vulnerability. Two major vulnerability factors in late-life depression are neuroticism and cardiovascular disease. Neuroticism yields a relative risk of 3.7 of becoming depressed in later life (Steunenberg et al, 2005). The prevalence of depression is significantly increased in patients with vascular disease, e.g. the cumulative 1-year incidence of depression was 39% in stroke patients and 25% in patients with myocardial infarction (Aben et al, 2002).

Both major risk factors have hardly been examined in relation to each other. Different hypotheses can be made as to how these factors act or interact. First, neuroticism and cardiovascular disease may act independently of each other. Second, such factors may interact with each other and increase the risk by more than the sum of both effects independently. A third, but more speculative hypothesis, is that of a negative interaction between high neuroticism and a higher prevalence of cardiovascular disease. A recent study of our group found that in elderly people aged 70 years and older, the effect of neuroticism on explaining depressive symptoms was attenuated by the presence of cerebrovascular disease (Wouts et al, 2011). Similarly, a small case-control study, also found a negative interaction between vascular risk and psychosocial vulnerability for depression (Oldehinkel et al, 2003). Although these findings may have been chance findings or ceiling effects of two important risk factors, one also may hypothesize that cerebrovascular disease causes apathy which in turn decreases the effect of neuroticism on depression (Wouts et al, 2011). This is in line with a previous finding of the Leiden 85+ study, showing that vascular risk factors were prospectively related to apathy, but not depression (Van der Mast et al, 2008). The effect of apathy however, might only be present in the very old population as studied by Wouts et al (2011) and Van der Mast et al (2008). Furthermore, cardiovascular disease was assessed by self-report of vascular events, whereas it is known that older people do have significant subclinical cerebrovascular damage indicated by white matter disease without ever experiencing a vascular event. It has been shown that subclinical vascular disease can be measured by the Intima Media Thickness (IMT) of the carotid artery and provide a good indicator of generalized atherosclerosis (Cheng et al 2002). Interestingly, IMT is correlated with both depressive disorder and symptoms (Tiemeier et al, 2004; Bus et al, 2010). Where

Van der Mast et al (2008) divided depression from apathy, Tiemeier et al (2004) did not. This could be an explanation why Tiemeier et al (2004) found the correlation between depression and atherosclerosis. Therefore, research is needed in which both the more sensitive IMT of the carotid artery is used as indicator of atherosclerosis whereas depression operationalized in more homogeneous symptom clusters. Previously, we showed that the somatic-affective symptoms of depression are specifically associated with a higher level of atherosclerotic disease (Bus et al, 2010) and with cardiovascular risk factors like visceral obesity (Marijnissen et al, 2011). On the other hand, cognitive-affective symptoms, like worrying or suicidal thoughts, may be more specifically associated with neuroticism. After all, cognitive reactivity, i.e. the ease with which particular patterns of negative thinking are reactivated in response to low mood, mediates the predisposing effects of neuroticism to depression (Barnhofer & Chittka, 2010; Boyle et al, 2010; Chapman et al, 2012; Merema et al, 2013; Hayward et al, 2013).

The present study was conducted to examine our hypothesis that neuroticism and subclinical atherosclerotic disease, as measured by IMT, negatively interact with regard to the presence of depressive symptoms in a population aged 50 through 70 years. We examined this hypothesis with respect to both, overall depressive symptoms as well as more homogeneous measures of depressive symptoms, including cognitive-affective and somatic-affective symptoms.

Methods

Sample

The present sample was drawn from the Nijmegen Biomedical Study (NBS), a population-based survey conducted in Nijmegen of people aged 20 through 90 years (Hoogendoorn et al, 2006). In 2004 and 2005 a questionnaire was sent to all participants (n=2807) in the age group 50 through 70 years. Of these persons 1517 (54%) gave additional informed consent to participate in a study on atherosclerosis. These participants visited the hospital for a detailed assessment of atherosclerotic disease, its risk factors and consequences (Holewijn et al, 2010). Exclusion criteria were a diagnosis of dementia or a history of stroke, because these conditions might directly affect the neurobiological brain circuits involved in depression (Alexopoulos, 2005). The Medical Ethics Committee of the Radboud University Nijmegen Medical Centre approved the study protocol.

Variables of interest

Carotid intima media thickness (IMT) - Carotid IMT was determined using semi-

automatic edge-detection software (M'AthSTD version 2.0,Metris, Argenteuil, France). IMT was defined as the mean IMT of four measured segments of the distal common carotid artery: far wall left, near wall left, far wall right and near wall right. Longitudinal images of the most distal 10 mm of both the far wall and the near wall of both common carotid arteries were obtained in the optimal projection (anterolateral, lateral or posterolateral). IMT was measured in an area free of plaque, which was defined as an area with an IMT ≥ 1.5 times the surrounding IMT. All measurements were carried out in end-diastole using the R-wave of a simultaneously recorded ECG as a reference frame. From each frame the mean IMT was calculated over at least 7.5 mm of the above mentioned 10 mm segment (yielding a quality index of at least 75%). The outcome variable was defined as the mean IMT of the near and far wall of both common carotid arteries. IMT measurements were performed after an overnight fast or in the afternoon 6 hours after a standardized breakfast. Participants were asked to abstain from caffeinated products for at least 12 hours and they were asked not to smoke for 12 hours before the visit. After standardizing the measurement conditions, there were no significant differences between the measurements performed in the morning and those performed in the afternoon (described elsewhere: Ter Avest et al, 2005). Participants were measured in supine position in a room with controlled temperature (23º - 24º C). The equipment used was a 7.5 MHz transducer of an AU5 ultrasound system (Esaote Biomedical, Genova Italy), connected to a computer with a data acquisition board. All measurements were highly standardized and performed by well-trained and certified sonographers. Reproducibility of our IMT-measurements was investigated and reported before as good (Ter Avest et al, 2005).

Depressive symptoms - Depressive symptoms were measured with the Beck Depression Inventory (BDI-I). The BDI-I is a 21-item self-report questionnaire with excellent psychometric characteristics (Beck et al, 1987). Each item is rated on a 0 to 3 scale, with 0 representing 'absence' and 1-3 representing increasing levels of severity of the symptom. The BDI-I yields a total score ranging from 0 to 63. Based on previous research in this field, a sum score ≥ 10 is indicative of clinically significant depressive symptoms (Marijnissen et al, 2011).

Neuroticism - Neuroticism was measured using the Dutch version of the revised Eysenck Personality Questionnaire (EPQ-RSS)(Eysenck et al, 1985). The EPQ-RSS yields a total score ranging from 0 to 12. Results of the Dutch version of this questionnaire strongly resemble those of the English version (Sanderman et al, 1991). The EPQ-RSS is based on a three-factor model of personality: neuroticism, extraversion and psychoticism. Neuroticism is a stable personality trait that also can be measured reliably in later life

because it is not significantly affected by physical health variables (Steunenberg et al, 2005). Nonetheless, an acute depression amplifies the personality profile of people prone to depression (Ormel et al, 2004). After recovery neuroticism decreases, but the overall shape of the profile does not change (Costa, Jr. et al, 2005; Santor et al, 1997). The relationship between change in personality and change in depressive symptoms is at most moderate and does not differ between men and women (Santor et al, 1997).

Covariates

Sociodemographic variables, a history of depression and health variables predict a large portion of elderly major and subsyndromal depression in the general population (Schoevers et al, 2000; Marijnissen et al, 2011). Therefore the following variables were examined as potential confounders: age, sex, living circumstances (together versus alone), higher education level, metabolic syndrome (MS), smoking status, physical activity, alcohol use, antidepressant use, cardiovascular medication, history of treated depression, coronary artery disease (CAD), and other chronic somatic diseases. MS was defined according to the International Diabetes Federation (IDF) (www.idf.org/webdata/docs/IDF-Meta_def_final.pdf, 2009). Individual components of the MS were measured; mean arterial pressure was measured using an oscillometric sphygmanometer (Criticon model no. 1846, Criticon Inc., FL). Waist circumference was measured at the level of the umbilicus. Triglycerides and glucose concentrations were determined using commercially available enzymatic reagents (AEROSET1 System, Abbott, Chicago IL). Smoking status, alcohol use, physical activity and cardio-vascular disease status were assessed during a short interview. Smoking behavior was categorized as current, former or never. Physical activity was based on the number of exercise sessions of more than 30 min moderate to vigorous activity per week (Stampfer et al, 2000). Because of a skewed distribution (that could not be normalized by transformation), a median split was used (0 or 1 v. 2 or more exercise moments/ week). Alcohol intake was dichotomized into severe use (>21 units for men and >14 units for woman) and non-severe use. CAD was assessed by a trained interviewer and defined as a history of treated angina pectoris, myocardial infarction, a history of percutaneous transluminal coronary angioplasty or coronary artery bypass grafting (Kriegsman et al, 1996). The chronic comorbid status was defined as the presence of one or more chronic co-morbid somatic diseases (yes/no). The self-reported presence of somatic disease was scored in case of current treatment for rheumatic disorder (or arthrosis), current treatment for COPD, current treatment for liver disease, current treatment for kidney disease, history or current treatment of morbus Crohn or colitis ulcerosis in history or history or current treatment of cancer. The history of treated lifetime depression was based on self-report data (yes/no). Medication use was defined by the use of at least half of the defined daily dose and based on medication

containers brought to the intervieuw. Eight different classes of medication were selected based on their potential influence on atherosclerotic disease and/or its association with depression and entered as dichotomies (yes/no). These classes were antidepressants (ATC N06AXXX), statins (ATC C10AXXX), angiotensin- converting enzyme (ACE) inhibitors (ATC C09AXXX), angiotensin II antagonists (C09CATC), Ca+-channel blockers (C08CXXX, C08DXXX, C08EXXX), beta- blockers (ATC C07AXXX), diuretics (C03XXXX), and analgesics (N02BAXX).

Statistical Methods

Because the BDI sum score had a skewed distribution in our sample, we applied a log-transformation in order to more closely approximate a normal distribution. All further analyses were conducted using the log-transformed sum score. IMT scores and neuroticism scores appeared to be normally distributed.

As described in a previous paper, principal components analysis (PCA) with oblimin rotation was conducted on the 21 individual BDI items to obtain fewer factors/components while retaining the original item information (Bus et al, 2010). In short, a two-factor solution appeared to be most optimal compared with the traditional two-factor structure of the BDI, i.e. a factor representing a cognitive- affective symptom cluster and factor representing a somatic-affective symptom cluster (Kaiser–Meyer–Olkin (KMO) measure of sampling adequacy: 0.898 ; Bartlett's test of sphericity : χ^2=5074, df=210, p<0.001, explained variance factor 1: 24.3 %; factor 2 : 7.6 %). The association between all primary dependent variables (BDI-I, cognitive-affective symptoms, somatic-affective symptoms) and independent (neuroticism, carotid IMT) were examined by pearson correlation test.

Subsequently, separate linear regression analyses were conducted with the different measures of depressive symptoms as the dependent variable, i.e. the log-transformed BDI sum score, the cognitive-affective symptom cluster and the somatic-affective symptom cluster. First, we examined the correlation between neuroticism and depression (Model 1). Second, we examined the correlation between the IMT and depression (Model 2). Third, we examined whether neuroticism and the IMT interacted in explaining the variance of depression (Model 3). All models were fully adjusted for the potential confounders described above.

All analyses were carried out using the Statistical Package for the Social Sciences (SPSS) version 17.0 (Inc. Chicago, IL).

Results

Of the 1517 subjects who consented to participation in the study of non-invasive measurements of atherosclerosis, 29 subjects were excluded because of a history of stroke. None of the participants was diagnosed with dementia. In addition, 238 (15.3%) subjects were excluded because of missing data caused by the folowing: not responding to the postal questionnaire containing the BDI (n=181); having three or more missing items on the BDI (n=36); missing data on the EPQ-RSS (n=11); or violating the rules for a reliable measurement of atherosclerotic disease (IMT) or its risk factors (i.e. having smoked before coming to the hospital, n=3; no adherence to non-fasting or light breakfast instructions n=2; and not stopping their lipid lowering medication (n=5).
Table 1 presents the characteristics of the final study population (n=1250). Subjects with missing data (238/1488, 16.0%) differed from subjects included with respect to mean (SD) age (62.3 (5.9) v. 61.0 (5.9) years, t=3.24, df=1492, p=.001), IMT (0.86 (0.13) v 0.84 (0.12) mm, t=2.31, df=1492, p=.021), but not with respect to sex (χ^2=0.1, df=1, p=.75), neuroticism (t=-0.2, df=1294, p=.86) and depressive symptoms (t=1.1, df=1259, p=.27).

The Pearson correlation (r) coefficient of the BDI sum score (after log-transformation) was 0.56 (df= 1247, p<.001) with the cognitive–affective symptom cluster and 0.87 (df=1247, p<.001) with the somatic-affective symptom cluster. Neuroticism was associated with both, the sum score of the BDI (r= 0.60, df=1248, p< .001), and the two depressive symptom clusters (cognitive-affective cluster, r= 0.58, df= 1247, p< .001; somatic-affective symptom cluster, r= 0.52, df=1247, p< .001). Finally, we found a significant but modest association between the BDI sum score and the IMT (r= 0.06, df=1248, p= .039). However, the IMT was only associated with the somatic-affective symptom cluster (r= 0.11, df=1247, p< .001), and not with the cognitive-affective symptom cluster (r= -0.05, df=1247, p=.06). Neuroticism and IMT were not significantly associated (r= 0.04, df=1248, p= .19).

As shown in Table 2, the above-described univariate associations between neuroticism and IMT values with the different measures of depression remained statistically significant in a multivariate regression model.
The association between cognitive-affective symptoms and IMT, which approached significance in the univariate analyses, completely lost significance after correction for confounders. Interestingly, we found a significant negative interaction term between the IMT and neuroticism in explaining the variance in the cognitive-affective symptoms (β= -.40, t=-2.66, df=1155, p= .008) but not with either the somatic-affective symptom cluster (β= -.06, t=-0.42, df=1155, p= .678) or the BDI total score (β= -24, t=-1.62, df=1155, p= .106).

Table 1 Baseline characteristics (n=1250).

Demographics	Descriptives	Values
• Age (years)	mean (SD)	61.0 (5.9)
• Male sex	n (%)	616 (49)
• Married or living together	n (%)	975 (78)
• Higher education	n (%)	510 (41)
Psychopathology		
• BDI sum score	median (IQR)	4.0 (2.0 – 8.0)
• BDI sum score ≥10	n (%)	206 (17)
• History of treated depression	n (%)	242 (19)
• Use of antidepressants	n (%)	47 (4)
• Neuroticism score	mean (SD)	3.4 (2.8)
Lifestyle factors		
• Smoking:	n (%)	
o Never		626 (50)
o Ever		410 (33)
o Current		212 (17)
• Severe alcohol usage	n (%)	146 (12)
• Physical activity	n (%)	462 (37)
Somatic co-morbidity		
• Intima media thickness (mm)	mean (SD)	0.84 (0.12)
• Metabolic syndrome (IDF)	n (%)	409 (33)
o Triglycerides (mmol/L)	mean (SD)	1.44 (0.82)
o HDL-cholesterol (mmol/L)	mean (SD)	1.41 (0.37)
o Waist circumference (cm)	mean (SD)	94.2 (12.3)
o Diastolic blood pressure (mmHg)	mean (SD)	78 (11)
o Systolic blood pressure (mmHg)	mean (SD)	128 (15)
o Fasting glucose (mmol/L)	mean (SD)	5.2 (0.9)
o Diabetes mellitus type 2	n (%)	74 (6)
• Coronary artery disease (yes/no)	n (%)	82 (7)
• Somatic co-morbidity (o or 1 versus ≥2)	n (%)	172 (14)
Cardiovascular medication		
• Diurectics	n (%)	139 (11)
• Beta blocker	n (%)	199 (16)
• Calcium antagonist	n (%)	44 (4)
• ACE inhibitor	n (%)	93 (7)
• Angiotensin II antagonist	n (%)	45 (4)
• Nitrate	n (%)	14 (1)
• Other	n (%)	24 (2)

Abbreviations: SD, standard deviation; n, number of participants; BDI, Beck Depression Inventory; IQR, Interquartile Range. IDF, International Diabetes Foundation; HDL, high-density lipoprotein

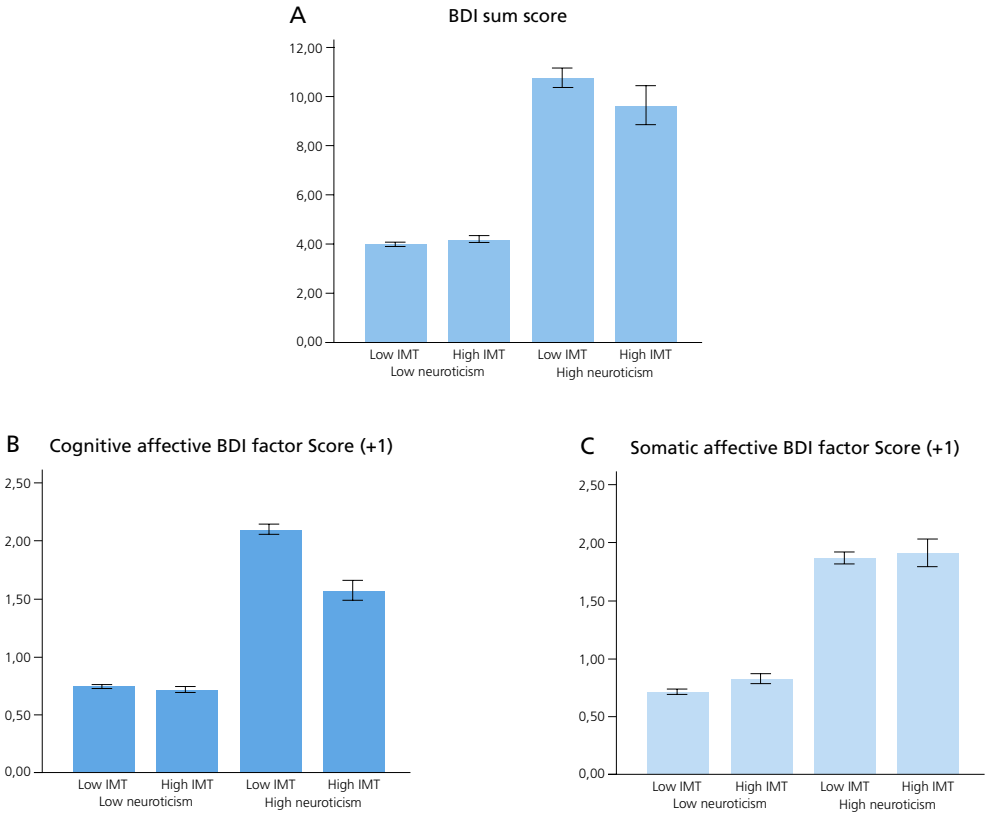
Table 2 Regression of neuroticism, intima-media thickness and their interaction on different measures of depressive symptoms assessed with the Beck Depression Inventory (BDI).

	BDI		Factor scores BDI			
	Log (sum score BDI)		Cognitive-affective		Somatic-affective	
	β	*P* value	*β*	*P* value	*β*	*P* value
Model 1 *						
Neuroticism	.54	<.001	.54	<.001	.45	<.001
Model 2 *						
Intima-media thickness (IMT)	.06	.040	-.02	.44	.10	.001
Model 3 * #						
Neuroticism	.54	<.001	.95	<.001	.44	<.001
IMT	.02	.49	.03	.54	.06	.022
Interaction neuroticism – IMT	*not significant*		-.40	.008	*not significant*	

* All linear regression analyses are based on a final sample of 1179 participants; significance of beta's are based on t-statistics, with 1157 degrees of freedom in model 1 and 2 and, 1155 in model 3 in case of a significant interaction term and 1156 in case the interaction term was not significant.
All models are adjusted for age, sex, married or living together, higher education, history of treated depression, use of antidepressants, smoking (dummy: never, ever, current), severe alcohol usage, sport moments, metabolic syndrome according to the IDF, presence of coronary artery disease, presence of chronic co-morbid somatic diseases, cardiovascular medication (antihypertensives, ACE inhibitors, calcium channel blockers, betablockers, nitrates, diurectics and analgesics.)
In case of non-significant interaction terms, the interaction term was removed from the model and runned again

In Figure 1, we have visualized the interaction effects between neuroticism and IMT by presenting the estimated marginal mean values of the different depressive symptoms scores adjusted for covariates and stratified by neuroticism score (highest quartile versus others) and IMT values (highest quartile versus others). Please note that the estimated marginal mean for the BDI sum score was calculated on the Log-transformed, whereas in the figure we present the inverse log (enabling interpretation of the absolute values).

Figure 1 Depressive symptom scores by IMT and neuroticism status (i.e. highest quartile vs others; bars represent estimated marginal mean values with error bars representing the 95% confidence interval based on the standard error of the mean).



Abbrevations: IMT, Intima Media Thickness; BDI, Beck Depression Inventory.

Statistics:

- All overall ANCOVAs are significant: for BDI sum score (F=75.7; df=3,1156; p<.001), for cognitive-affective BDI factor score (F=102.5; df=3,1156; p<.001), and for somatic-affective BDI factor score (F=67.2; df=3,1156; p<.001).
- Post-hoc t-tests restricted to subjects with high neuroticism scores, showed that subjects with high IMT values differed significantly from those with low IMT values with respect to the BDI sum score (t=3.05, df=239, p=.003) and the cognitive-affective BDI factor score (t=11.10, df=239, p< .001), but not with respect to the somatic-affective BDI factor score (t=-0.75, df=239, p= .46).

Discussion

Main findings

Neuroticism is strongly associated with the total number of depressive symptoms, and with both cognitive-affective and somatic-affective symptoms, whereas the somatic affective symptom cluster specially drives the association between depression and subclinical atherosclerosis. Nevertheless, we found a negative interaction between neuroticism and atherosclerosis in explaining the cognitive-affective symptoms of depression. In line with our hypothesis, the effect of neuroticism in explaining depressive symptoms diminishes in the presence of more severe atherosclerosis. A possible explanation for these results is the hypothesis that cerebrovascular disease may cause apathy, which in turn decreases the association between neuroticism and depression. Below we will discuss this hypothesis in context of previous findings in the literature.

Comparison with the literature

The vascular depression hypothesis has stimulated research into the biological predictors of late-life depression, thereby often paying less attention to other theories of depression (Sneed et al, 2011). Neuroticism is strongly related to depression (Kendler et al, 2006), although limited data are available with respect to middle aged and older people (Steunenberg et al, 2005). Interestingly, our results show that the association between neuroticism and the somatic-affective symptom cluster is of similar strength as the association between neuroticism and the cognitive-affective symptom cluster. Because previous studies show that neuroticism is not significantly affected by physical health (Steunenberg et al, 2005), we may conclude, having corrected for somatic comorbidity, that neuroticism is associated with those somatic symptoms that are intrinsically part of the depressive syndrome. Nevertheless, neuroticism only interacted with atherosclerosis in the association with cognitive-affective symptom cluster. We hypothesize this to be caused by apathy due to cerebrovascular atherosclerosis. Neuroticism is a trait-characteristic that closely resembles the cognitive domain of depression. This contributes to the strong correlation between neuroticism and depressive symptoms. Nevertheless, in case of a higher level of atherosclerosis, the association between neuroticism and cognitive-affective symptoms becomes less pronounced (Wouts et al, 2011). We hypothesize this to be due to apathy as a result of vascular damage to the frontostriatal pathways (Kim et al, 2011; Murakami et al, 2013). Support for this second possibility is provided by comparable results found by our group in another sample (Wouts et al, 2011) and by the fact that levels of neuroticism were less pronounced in late-onset compared to early-onset late-life depression (Sneed et al, 2011).

The relationship between atherosclerosis, depression and apathy is complicated and has relatively rarely been studied. In 1997, two research groups independently proposed the vascular depression hypothesis (Alexopoulos et al, 1997; Krishnan et al,1997). This hypothesis postulates that cerebrovascular disease may predispose, precipitate, or perpetuate some geriatric depressive syndromes. Until now, the evidence for a real distinctive disorder remains limited with many inconsistent results (Baldwin et al, 2005). Most likely, cerebrovascular disease, especially deep white matter hyperintensities are associated with neuropsychological deficits, which not only predispose elderly people to depression, but also shape the depressive phenotype. Decreased processing speed and executive dysfunctioning have been identified as the two underlying neuropsychological core deficits (Sheline et al, 2008). Subsequently, the depression executive dysfunction (DED) syndrome has been introduced (Alexopoulos, 2005), validated by both treatment resistance of the DED syndrome (Alexopoulos et al, 2004) and by persisting cognitive deficits in case of remitted depression (Kohler et al, 2010). Executive dysfunction, however, has been consistently linked with atherosclerosis and vascular disease (Lamar et al, 2009/2010). Interestingly, directly after launching the vascular depression hypothesis in the literature, it has been suggested that vascular brain disease would be more specific for apathy than for depression (Fones et al, 1998). Although the association between executive functioning and apathy has hardly been examined, both constructs appear to be associated with each other in Alzheimer's disease (Esposito et al, 2010). Interestingly, in line with our findings, Archer et al (2007) found that the presence of Alzheimer's disease attenuated the association between neuroticism and depression.

Studies examining both depression and apathy in relation to vascular disease show a relationship with both syndromes (Withall et al, 2011) or with apathy only (Van der Mast, 2008; Sugawara et al, 2010). Atherosclerosis at baseline did not predict incident depression in older adults in a large prospective, population-based study (Newson et al, 2010). We propose that cerebrovascular disease will lead to neuropsychological deficits that are more specifically linked with apathy than with depressed mood per se.

Methodological considerations

The strengths of the present study are the large sample size and reliable measures of depressive symptom clusters and subclinical atherosclerotic disease in middle-aged and older people at risk of cerebrovascular disease but prior to clinical stroke.

As explanation for our findings we postulate a hypothesis of vascular apathy. Unfortunately, apathy was not directly measured and to our knowledge, the relationship between cognitive-affective symptoms of depression and apathy has not been studied yet. From a clinical perspective, it is conceivable that apathy is associated with indif-

ference and lower cognitive activity like rumination, worrying or suicidal thoughts. On the other hand, we also need to acknowledge that the absence of cognitive-affective symptoms in apathy is only part of the apathy-syndrome as recently defined by consensus (Robert et al, 2009). Some minor limitations should be addressed. First, we assessed the IMT as measure for generalised atherosclerosis. Although it is assumed that the IMT in the common carotid arteries is highly associated with cerebrovascular disease (Cao et al, 2003) we did not directly assess (subclinical) cerebrovascular disease by neuroimaging. Nonetheless, IMT is widely used as a surrogate marker of subclinical atherosclerosis nowadays. Several studies reported about the predictive value of IMT in cardiovascular risk stratification and IMT has been depicted as a strong predictor of future vascular events (see Holewijn et al, 2009). Second the cross-sectional design of this study does not allow our results to be interpreted causally. To date, no prospective studies are available relating neuroticism and vascular disease to depressive symptoms or symptoms clusters in concert. Third, we used a population sample, so bias towards the most healthy people may have occurred, resulting in less (advanced) atherosclerosis and depressive symptoms. This may have resulted in less overall variance of the atherosclerosis and depression measures and also lowered the variance explained by the factors found.

Final conclusion and clinical implications

The present study illustrates the complexities of late-life depression on different levels. Within the clinical setting depression and apathy can be hard to distinguish and may frequently overlap. Research paradigms on late-life depression, shift from the importance of vascular disease to more complex neuropsychological deficits (especially executive dysfunctions) (Alexopoulos, 2005). Nevertheless, within an randomized controlled trial on late-life depression, both vascular disease and executive dysfunction were correlated as well as independently associated with a worse prognosis and slower time to response (Alexopoulos et al, 2004). As shown by our study, personality traits like neuroticism should be included in examining late-life depression as the strong relationship between neuroticism and depression changes dependent on the presence of vascular disease, probably due to the emergence of apathy.

References

Aben I, Denollet J, Lousberg R et al. (2002) Personality and vulnerability to depression in stroke patients: a 1-year prospective follow-up study. *Stroke;* 33(10):2391-2395.

Alexopoulos GS, Meyers BS, Young RC et al. (1997) 'Vascular Depression' hypothesis. *Arch Gen Psychiatry;* 54(10):915-922.

Alexopoulos GS, Kiosses DN, Murphy C et al. (2004) Executive dysfunction, heart disease burden and remission of geriatric depression. *Neuropsychopharmacology;* 29 (120):2278-84

Alexopoulos GS. (2005) Depression in the elderly. *Lancet;* 365:1961-1970.

Archer N, Brown RG, Reeves SJ et al. (2007) Premorbid personality and behavioral and psychological symptoms in probable Alzheimers disease. *Am J Geriatr Psychiatry;* 15(3):202-213.

Baldwin RC. (2005) Is vascular depression a distinct sub-type of depressive disorder? A review of causal evidence. *Int J Geriatr Psychiatry;* 20(1):1-11.

Barnhofer T and Chittka T. (2010) Cognitive reactivity mediates the relationship between neuroticism and depression. *Beh Research and Therapy;* 48:275-281.

Beck AT, Steer RA. Manual for the Revised Beck Depression Inventory 1. San Antonio, Tex. Psychological corporation.

Beekman ATF, Copeland JRM, Prince MJ. (199) Review of community prevalence of depression in later life. *British Journal of Psychiatry;* 174:307-311.

Boyle LL, Lyness JM, Duberstein PR et al. (2010) Trait neuroticim, depression, and cognitive function in older primary care patiente. *Am J Geriatr Psychiatry;* 18(4):305-12.

Bus BA, Marijnissen RM, Holewijn S et al. (2010) Depressive symptom clusters are differentially associated with atherosclerotic disease. *Psychol Med;* 10:1-10.

Cao JJ, Thach C, Manolio TA et al. (2003) C-Reactive Protein, Carotid Intima-Media Thickness, incidence of ischemic stroke in the elderly. The cardiovascular health study. *Circulation;* 108: 166-170

Chapman B, Duberstein P, Tindle HA et al. (2012) Personality Predicts Cognitive Function over 7 years in older persons. *Am J Geriatr Psychiatry;* 20(7):612-621.

Cheng SW, Ting AC, Wu LL. (2002) Ultrasonic analysis of plaque characteristics and intimal-medial thickness in radiation-induced atherosclerotic carotid arteries. *Eur J Vasc Endovasc Surg;* 24 (6):499-504.

Costa PT Jr, Bagby RM, Herbst JH et al. (2005) Personality self-reports are concurrently reliable and valid during acute depressive episodes. *J Affect Disord;* 89(1-3):45-55.

Esposito F, Rochat L, Juillerat Van der Linden AC et al. (2010) Apathy and executive dysfunction in Alzheimer disease. *Alzheimer dis Assoc Disord;* 24(2):131-137.

Eysenck SBG, Eysenck HJ, Barrett P. (1985) A revised version of the Psychoticism Scale. *Person Individ Diff;* 6(1):21-29.

Fales CL, Barch DM, Rundle MM et al. (2008) Altered emotional interference processing in affective and cognitive-control brain circuitry in major depression. *Biol Psychiatry;* 63(4):377-384.

Fones CSL (1998) Distinguishing apathy syndromes from vascular depression. *Arch gen psychiatry;* 55:844.

Hayward RD, Taylor WC, Smoski MJ et al. (2013) Association of Five-Factor Model personality domains and facets with presence, onset, and treatment outcomes of major depression in older adults. *Am J Geriatr Psychiatry;* 21(1):88-96.

Hoogendoorn EH, Hermus AR de Vegt F et al. (2006) Thyroid function and prevalence of anti-thyroperoxidase antibodies in a population with borderline sufficient iodine intake: influences of age and sex. *Clinical Chemistry;* 52:104-111.

Holewijn S, den Heijer M, Swinkels DW et al. (2009) Brachial artery diameter is related to cardiovascular risk factors and intima-media thickness. *European Journal of Clinical Investigation;* 39:554-560.

Kendler KS, Gatz M, Gardner CO et al. (2006) Personality and major depression: a Swedish longitudinal, population-based twin study. *Arch Gen Psychiatry;* 63(10):1113-1120.

Kim BS, Lee DH, Lee DW et al. (2011) The role of vascular risk factors in the development of DED syndrome among an elderly community. *Am J Geriatr Psychiatry;* 19(2):104-114.

Köhler D, Thomas AJ, Lloyd A et al. (2010) White matter hyperintensities, cortisol levels, brain atrophy and continuing cognitive deficits in late-life depression. *The British Journal of Psychiatry;* 196:143-149.

Kriegsman DM, Penninx BW, van Eijk JT et al. (1996) Self-reports and general practitioner information on the presence of chronic diseases in community dwelling elderly. A study on the accuracy of patients'self-reports and on determinants of inaccuracy. *Journal of Clinical Epidemiology;* 49:1407-1417.

Krishnan KR, Hays JC, Blazer DG. (1997) MRI-defined vascular depression. *Am J Psychiatry;* 154(4):497-501.

Lamar M, Price CC, Giovannetti T et al. (2009/10) The dysexecutive syndrome associated with ischaemic vascular disease and related subcortical neuropathology: a Boston Process Approach. *Behavioural Neurology;* 22:53-62.

Marijnissen RM, Bus BA, Holewijn S et al. (2011) Depressive symptom clusters are differentially associated with general and visceral obesity. *J. Am Geriatr Soc;* 59(1):67-72.

Merema MR, Speelman CP, Foster JK et al. (2013) Neuroticim (not depressive symptoms) predicts memory complants in some community-dwelling older adults. *Am J Geriatr Psychiatry;* 21(8): 729-36.

Murakami R, Hama S, Yamashita H et al. (2013) Neuroanatomic Pathways associated with poststroke affective and apathetic depression. *Am J Geriatr Psychiatry;* 21(9):840-7.

Newson RS, Hek K, Luijendijk HJ et al. (2010) Atherosclerosis and incident depression in late life. *Arch Gen Psychiatry;* 67 (11):1144-1151.

Oldehinkel Aj, Ormel J, Brilman EI et al. (2003) Psychosocial and vascular risk factors of depression in later life. *J Affect Disord;* 74(3):237-246.

Ormel J, Oldehinkel AJ, Vollebergh W. (2004) Vulnerability before, during and after a major depressive episode: a 3-wave population based study. *Arch Gen Psychiatry;* 61(1):990-996.

Robert P, Onyike CU, Leentjens AF et al. (2009) Proposed diagnostic criteria for apathy in Alzheimer's disease and other neuropsychiatric disorders. *Eur Psychiatry;* 24(2):98-104.

Sanderman R, Eysenck SBG, Arrindell WA. (1991) Cross-cultural comparisons of personality: the Netherlands and England. *Psychological Reports;* 69:1091-1096.

Santor DA, Bagby RM, Joffe RT. (1997) Evaluating stability and change in personality and depression. *J Pers Soc Psychol;* 73(6):1354-1362.

Schoevers RA, Beekman AT, Deeg DJ et al. (2000) Risk factors for depression in later life; results of a prospective commuinty based study (AMSTEL). *J Affect disord;* 59(2):127-137.

Sheline YI, Barch DM, Garcia K et al. (2006) Cognitive function in late life depression: relationships to depression severity, cerebrovascular risk factors and processing speed. *Biol Psychiatry;* 60(1):58-65.

Sneed JR, Culang-Reinlieb ME. (2011) The vascular depression hypothesis: an update. *Am J Geriatr Psychiatry;* 19(2):99-103.

Stampfer MJ, Hu FB, Rimm EB et al. (2000) Primary prevention of coronary heart disease in women through diet and lifestyle. *N Engl J Med;* 343:16-22.

Steunenberg B, Twisk JW, Beekman AT et al. (2005) Stability and change of neuroticism in aging. *J Gerontol B Psychol Sci Soc Sci;* 60(1):27-33.

Sugawara N, Yasui-Furukori N, Umeda T et al. (2011) Ankle brachial pressure index as a marker of apathy in a community-dwelling population. *Int J Geriatr Psychiatry;* 26:409-414.

Ter Avest E, Holewijn S, Stalenhoef AF et al. (2005) Variation in non-invasive measurements of vascular function in healthy volunteers during daytime. *Clinical Science (London);* 108:425-431.

Tiemeier H, van Dijck W, Hofman A et al. (2004) Relationship between atherosclerosis and late-life depression; the Rotterdam Study. *Arch gen Psychiatry;* 61:369-376.

Van de Mast RC, Vinkers DJ, Stek ML et al. (2008) Vascular disease and apathy in old age. The Leiden 85-plus Study. *Int J Geriatr Psychiatry;* 23(2):266-271.

Withall A, Brodaty H, Altendorf A et al. (2010) A Longitudinal study examining the independence of apathy and depression after stroke: the Sydney Stroke Study. *International Psychogeriatrics;* 23(2):264-273.

Wouts L, Janzing JG, Lampe IK et al. (2011) The interaction between cerebrovascular disease and neuroticism in late-life depression: a cross-sectional study. *Int J Geriatr Psychiatry;* 26:702-710.

Late-life depression in context of low neuroticism is risk factor for stroke: a 9-year cohort study

In press

Depression in context of low neuroticism is risk factor for stroke: a 9-year cohort study

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Abstract

Objectives – Depression predicts stroke, however meta-analyses show significant heterogeneity. We hypothesise that the risk of depression on incident stroke is conditional upon the relative contribution of vascular disease and of neuroticism in the underlying pathways to depression in a specific patient. We examined whether depression increases stroke in persons with low neuroticism and without pre-existing cardiac disease

Methods – Population-based cohort study with 9-year follow-up (n=2050; ≥ 55 years, 52% female). The incidence of stroke was determined by self-report data as well as data from general practitioners and death-certificates. Neuroticism was measured using the Dutch Personality Questionnaire (DPQ) and depression using the Center for Epidemiological Studies-Depression Scale (CESD). All data were analysed by Cox proportional hazards regression.

Results – 117 incident cases of stroke occurred during follow-up. Among persons with a history of cardiac disease (n=401), depression predicted incident stroke independent of neuroticism-level with a hazard rate (HR) of 1.05 [95% CI: 1.01 – 1.10] (p=.02). In persons without cardiac disease (n=1649), depression and neuroticism interacted significantly in predicting incident stroke (p=.028). Stratified analyses showed that depression predicted incident stroke in those with low neuroticism: HR =1.05 [95% CI: 1.00 – 1.09] (p=.033), but not in those with high neuroticism: HR =1.01 [95%: 0.96 – 1.05] (p=.82).

Conclusions - In persons without pre-existent cardiac disease, depression is only predictive for future stroke in absence of high neuroticism. This might be explained by the hypothesis that late-life depression in context of low neuroticism is a marker of subclinical vascular disease.

Keywords

Stroke; Subclinical vascular disease; Cardiac disease; Depression; Neuroticism.

Introduction

Late-life depression is not only a common and disabling condition in later life, it also predicts the onset of major medical illnesses, such as stroke (van der Kooy et al, 2007; Wouts et al, 2008; Taylor et al, 2013; Valkanova et al, 2013). Depression is driven by multiple etiological factors, including personality (such as neuroticism) (Steunenberg et al, 2006) and vascular factors (Sneed et al, 2008; Ormel et al, 2011; Taylor et al, 2013). Especially among older people, both of these pathways may act to a certain degree in individual patients. Therefore, the degree to which depression is a predictor of incident stroke might be conditional on the relative weight of vascular disease (so called 'vascular depression') and of neuroticism (so called 'neurotic-depression') as the underlying pathways to depression.

Meta-analyses indeed show that late-life depression is prospectively associated with stroke (Pan et al, 2011; Valkanova et al, 2013). Nonetheless, the same meta-analyses point to significant heterogeneity across studies (Pan et al, 2011), which has not been explained properly yet (Pan et al, 2011). Recently, it was found that depression in the oldest-old does not increase stroke risk, but still is a risk factor for all-cause mortality (Kohler et al, 2013). The effects of depression on stroke risk may be due to residual confounding by the severity of subclinical vascular disease (de Jonge et al, 2012). Many older persons without a history of ischaemic heart disease or stroke do have a significant level of vascular pathology in the presence of generalised atherosclerosis. Recently, we have shown that the intima media thickness of the carotid artery, a marker for generalised atherosclerosis, is associated with depressive symptoms, even in the absence of a history of vascular events (Bus et al, 2011). This association, however, was confined to the somatic-affective symptoms domain of depression, which may indeed point to overlap or confounding between subclinical vascular disease and depression (Bus et al, 2011). Interestingly, incident depression after a myocardial infarction also predicted a poorer prognosis of heart disease, whereas recurrent depression as well as depression associated with a high level of neuroticism did not (Spijkerman et al, 2005; de Jonge et al 2006; Dickens et al, 2008). These findings fit with the hypothesis that the risk of depression on future vascular events is conditional upon depressive symptoms related to underlying vascular disease and not upon 'neuroticism-associated' depression.

In the Longitudinal Aging Study Amsterdam (LASA), we have shown that depression only predicted incident stroke in older persons with pre-existing cardiac disease (Wouts et al, 2008). A logical explanation would be that in non-cardiac patients the contribution of vascular disease burden to depression is minimal and other pathways like high levels

of neuroticism may be more important. Nonetheless, this explanation does not fully fit with the abovementioned findings that depression is also associated with subclinical vascular disease (Bus et al, 2011). The present study, therefore, is an extension of our previous findings in LASA (Wouts at al, 2008).
We assume that the association between depression and vascular events is confounded by underlying vascular disease in later life and that this may differ for different subtypes of depression (vascular versus neurotic-associated depression). The aim of this study was to examine whether a lower level of neuroticism in depressed older persons without pre-existing cardiac disease indeed would be associated with an increased risk of stroke in LASA. We a priori hypothesise that vascular depression, defined theoretically by a high aetiological contribution of vascular disease, increases the risk on future strokes, whereas 'neuroticism-associated' depression does not.

Methods

Study design and population
This study was performed as part of the Longitudinal Aging Study Amsterdam (LASA). LASA is a prospective cohort study focusing on physical functioning and wellbeing of an older (≥ 55 years) population (N=3107). LASA started in 1992/93, with follow-up measurements every three years and its methods have been described in more detail elsewhere (see Beekman et al, 1995; Beekman et al, 2002). For this particular study 9 years of follow-up data were available. Eligible were those participants without a history of stroke (n=3018, 97.1%) allowing us to study incident stroke and availability of baseline data on depressive symptoms (missing for 51 participants) and stroke (missing for 2 participants). Of these 2965 eligible LASA participants, 915 participants had no data on neuroticism, leaving a final sample of 2050 participants. The number of missing measurements on neuroticism was high because of the method of measurement: participants were asked to return a self-report questionnaire on neuroticism after being interviewed. Table 1 presents the baseline characteristics for those participants with and without data on neuroticism.

Standard protocol approvals, registrations, and patient consents
All participants of LASA completed an informed consent after oral and written information. The Medical Ethics committee of the VU University Medical Center approved the study design and procedures.

Variables of interest

Stroke morbidity and mortality - Non-fatal stroke was assessed using an algorithm based on the 3-yearly prospective interviews and GP-information (as in the Netherlands all patients are linked to only one GP who receives all medical information from specialists). Previously, a LASA-study showed that self-report information on stroke was reasonably moderately accurate when compared with GP-information (concordance: kappa=0.56; CI 0.48-0.64) and that concordance did not covary with level of depressive symptoms of patients (Kriegsman et al, 1996). We considered a stroke to have occurred if self-reported and GP information was consistent or if a medical specialist had confirmed the GP diagnosis of stroke.

Fatal stroke was defined as an ICD-9 codes 431, 433, 434 and 436 and ICD-10 codes I-61,I-63 and I-64 on the death certificates registered by the Netherlands Central Bureau of Statistics. These were 100% complete.

The primary outcome, time to stroke, is calculated for non-fatal stroke as the time between baseline and halfway the year for which the stroke has been reported, for fatal stroke the exact time between baseline and death.

Depression - Depressive symptoms were measured using the self-report Center for Epidemiologic Studies Depression scale (CESD). All 20-items refer to the past-week and are scored on a 4-point scale (range sum score 0-60). The psychometric properties of the scale were found to be good in older populations and overlap with symptoms of physical illness is minimal (Beekman et al, 1997). A score of ≥16 indicates clinically relevant depressive symptoms (Beekman et al, 1997). In LASA, the cut-off of 16 or higher had a sensitivity of 100% and a specificity of 88% for major depressive disorder according to DSM-IV-criteria (Berkman et al, 1986).

Neuroticism - Neuroticism is a personality trait that is stable across the life span and not affected by physical health status (Steunenberg et al, 2007). People with a high level of neuroticism are sensitive to negative stimuli (Tellegen et al, 1985), causing emotional instability and negative moods like anxiety, sadness, guilt, hostility and self-dissatisfaction(Watson et al, 1984; Steunenberg et al, 2007). Neuroticism was measured using the Dutch Personality Questionnaire (DPQ) (Luteijn et al, 2000). Pilot-studies before LASA started showed that the original scale of 36 items could be abbreviated without loss of validity or reliability (Smits et al, 1995; Steunenberg et al, 2003). These DPQ items have strong negative relations with the Emotional Stability-Scale of the NEO-PI-R (Luteijn et al, 2000). The DPQ asks respondents if statements apply to them; possible answers are yes/do not know/ no. Scores range between 0 and 50.

Cardiac disease - As previously decribed (Wouts et al, 2008); 'Cardiac disease was defined as myocardial infarction, congestive heart failure, angina pectoris, or cardiac arrhythmia and established at baseline using an algorithm used earlier in LASA (Bremmer et al, 2006). This algorithm uses 3 sources of information: self-reported, medication, and GP information. We considered only 1 confirmative source necessary for diagnosis because self-reported cardiac disease is sufficiently accurate in LASA (concordance with GP: κ=0.69; 95% CI, 0.65-0.73) (Beekman et al, 1997). '

Covariates

Age, sex, general health-related variables (functional limitations and cognitive impairments) and established stroke risk factors (smoking, obesity, diabetes mellitus, hypertension) were considered potential confounders and as such included in the analyses (Berkman et al, 1986).

Functional limitations were scored as none, 1 or ≥2, using a 3-item questionnaire (van Sonsbeek et al 1988). Cognition was measured with the Mini Mental State Examination (MMSE) (Folstein et al, 1975). The variable smoking included current smoking. Obesity was defined as a body mass index of 30 kg/m^2 or greater (Ogden et al, 2007). Diabetes mellitus (yes/no) was based on self-report data, the use of antidiabetic agents or a GP diagnosis (Kriegsman et al, 1996). Blood pressure (mmHG) with an oscillometric blood pressure monitor (model HEM-706; Omron Corporation, Tokyo, Japan) after 5 minutes of rest. Out of the three measurements, a mean systolic blood pressure of 140-159 mm Hg or a mean diastolic blood pressure of 90-99 mm Hg was categorized as stage 1 hypertension. A mean systolic blood pressure of ≥ 160 mm Hg or a mean diastolic blood pressure of ≥ 100 mm Hg was categorized as stage 2 hypertension (Chobanian et al, 2003). Antidepressant use was established by visually checking all of the participants' medications during interview at their homes.

Statistical methods

Differences between groups were explored by calculating descriptive statistics (e.g. means, standard deviations, frequencies) and performing t-tests for continuous measures with normal distributions, Mann-Whitney U-tests for continuous measures with skewed distributions and Chi-Square tests for categorical variables.

We checked the primary variables for normality, collinearity and proportionality of hazards. Neuroticism was not normally distributed, therefore we classified respondents as low or high on neuroticism based on the median split (< ≥5) in order to prevent that influential outliers cause results. We also performed sensitivity analyses by repeating all analyses on the log-transformed continuous neuroticism score.

The predictive effect of depression on incidence of stroke was tested with multiple

Cox-regression analyses with time to a fatal or non-fatal stroke as the dependent variable and corrected for age, sex, global cognitive functioning (MMSE-score), one or more functional limitations, smoking, hypertension (stage 1 or 2), diabetes mellitus, and obesity. Depression was examined both as a continuous measure based on the CESD total sum score as well as dichotomised (≥16), indicative of clinically relevant depressive symptoms.

We first checked for an interaction between depression and the presence of cardiac disease using Cox-proportional hazards regression models with stroke as the dependent variable. In the fully adjusted models, the hazard rate (HR) for clinically relevant depressive symptoms by cardiac disease status was 4.03 [95% confidence interval (CI): 1.22 – 13.28] (p=.022) and HR for severity of depressive symptoms by cardiac disease status was 1.06 [95% CI: 1.01 – 1.11] (p=.032). Therefore, all analyses will be stratified for baseline cardiac disease status.

For the objective of the present chapter we examined interaction terms between depression and neuroticism on incidence of stroke when stratified for pre-existing cardiac disease using multiple Cox-regression analyses. In case of significant interactions with neuroticism, results will be presented separately for participants with low and high neuroticism scores. All analyses were conducted in SPSS for Mac, 2011. We considered p-values <.05 as significant.

Results

Baseline characteristics

The mean (SD) age of the 2050 study participants was 69.3 (8.5) years and 1046 (51.0%) were women (see Table 1). At baseline 261 (12.7%) participants suffered from clinically relevant depressive symptoms, whereas the median neuroticism score was 4.0 (interquartile range 7.0). A total of 117 incident strokes occurred during follow-up, resulting in an overall stroke rate of 7.0 per 1000 person years. Table 2 presents the baseline characteristics by cardiac disease status.

Results by level of neuroticism

Table 3 shows the effect of depression and neuroticism on the onset of stroke in patients with and without cardiac disease separately. Adjusted for covariates, the interaction term of neuroticism (median split) by depression was only significant in patients without cardiac disease.

Removing the interaction term from analyses within those participants with cardiac disease (n=401) showed that depression predicted incident stroke (HR depressive

Table 1 Characteristics of included patients versus those with missing data on neuroticism.

Characteristic		Included (n=2050)	Excluded (n=915)	Statistics
Age (years)	Mean (SD)	69.3 (8.5)	73.2 (8.6)	t=11.3, df=2963, p<.001
Female sex	n (%)	1046 (51.0)	500 (54.6)	χ^2=3.3, df=1, p=.068
Cognitive functioning (MMSE score)	Mean (SD)	27.5 (2.3)	25.9 (3.6)	t=-12.7, df=2963, p<.001
Depressive symptoms (CESD score)	Mean (SD)	7.4 (7.4)	8.9 (8.4)	t=4.8, df=2963, p<.001
One or more functional limitations	n (%)	728 (35.7)	445 (49.3)	χ^2=48.2, df=1, p<.001
Smoking (yes)	n (%)	477 (24.4)	171 (27.7)	χ^2=2.7, df=1, p=.098
Stage 1 or 2 hypertension	n (%)	479 (24.9)	144 (23.6)	χ^2=0.4, df=1, p=.528
Cardiac disease	n (%)	401 (19.6)	210 (23.0),	χ^2=4.4, df=1, p=.035
Diabetes mellitus	n (%)	224 (10.9)	134 (14.7)	χ^2=8.3, df=1, p=.004
Obesity	n (%)	323 (17.6)	134 (21.6)	χ^2=5.1, df=1, p=.024
Use of antidepressants	n (%)	37 (1.9)	12 (1.9)	χ^2=0.0, df=1, p=.946
Incident stroke	n (%)	117 (5.7),	59 (6.4)	χ^2=0.6, df=1, p=.430

Abbrevations: SD, standard deviation; n, number of participants; MMSE, Mini Mental State Examination; CESD, Center for Epidemiologic Studies Depression scale.

Table 2 Characteristics of included patients by cardiac disease status.

Characteristic		No cardiac disease (n=1649)	Cardiac disease (n=410)	Statistics
Age (years)	Mean (SD)	68.6 (8.4)	72.4 (8.3)	t=-8.1, df=2048, p<.001
Female sex	n (%)	889 (53.9)	157 (39.2)	χ^2=28.1, df=1, p<.001
Cognitive functioning (MMSE score)	Mean (SD)	27.5 (2.3)	27.2 (2.4)	t=2.7, df=2048, p=.007
Depressive symptoms (CESD score)	Mean (SD)	7.1 (7.2)	8.9 (8.3)	t=-4.4, df=2048, p<.001
Neuroticism (DPQ score)	median (IQR)	4.0 (7.0)	5.0 (9.0)	Z=-2.4, p=.018
One or more functional limitations	n (%)	520 (31.7)	208 (52.4)	χ^2=59.6, df=1, p<.001
Smoking (yes)	n (%)	384 (24.6)	93 (23.8)	χ^2=0.1, df=1, p=.752
Stage 1 or 2 hypertension	n (%)	398 (25.8)	81 (21.0)	χ^2=3.8, df=1, p=.052
Diabetes mellitus	n (%)	159 (9.6)	65 (16.2)	χ^2=14.3, df=1, p<.001
Obesity	n (%)	251 (17.0)	72 (20.1)	χ^2=2.0, df=1, p=.160
Use of antidepressants	n (%)	32 (2.0)	5 (1.3)	χ^2=1.0, df=1, p=.319
Incident stroke	n (%)	85 (5.2)	32 (8.0)	χ^2=4.8, df=1, p=.029

Abbrevations: Standard deviation; n, number of participants; MMSE, Mini Mental State Examination; CESD, Center for Epidemiologic Studies Depression scale; DPQ, Dutch Personality Questionnaire; IQR, Interquartile Range.

symptoms = 1.05 [95% CI: 1.01 – 1.10], p=.020; HR clinically relevant depressive symptoms = 2.08 [95% CI: 0.93 – 4.63], p=.075, respectively), whereas neuroticism did not (HR= 1.06 [95%: 0.47 – 2.38], p=.88 and HR = 1.23 [95% CI: 0.57 – 2.68], p=.60, respectively). Neuroticism was not identified as an independent predictor of stroke risk in any of the models (all p-values >.05).

Stratified analyses by neuroticism status in participants without cardiac disease (n=1649), showed that when adjusted for covariates depression predicted incident stroke in those with low neuroticism (n=838): HR depressive symptoms = 1.05 [95% CI: 1.00 – 1.09] (p=.033) and HR clinically relevant depressive symptoms = 4.53 [95% CI: 1.72 – 11.9] (p=.002), respectively, but not in those with high neuroticism (n=811): HR depressive symptoms = 1.01 [95%: 0.96 – 1.05] (p=.82) and HR clinically relevant depressive symptoms = 0.78 [95% CI: 0.30 – 2.06] (p=.62), respectively. See Figure 1. Figure 1 presents the absolute stroke rates per 1000 person years by depression and neuroticism status in patients with no cardiac history (n=1649).

Stratifying on dichotomised CESD-scores and neuroticism scores (as done for figure 1) results in low numbers per group. In the non-depressed group (n=1463), 5.2% (42/805) of persons with low neuroticism had an incident stroke and 5.0% (33/658) of persons with high neuroticism. In the depressed group (n=186), 15.2% (5/33) of persons with low neuroticism had an incident stroke and 3.3% (5/153) of persons with high neuroticism.

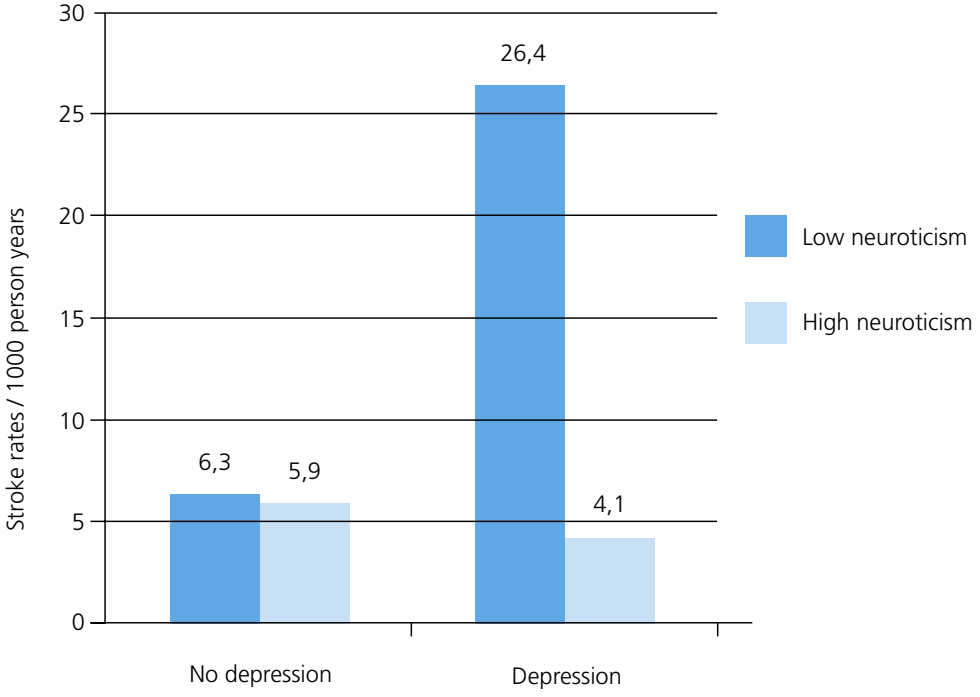
As dichotomised data are more prone for chance findings, we also re-analysed the data using 10Log transformation of neuroticism and the sum score of the CESD. These analyses fully supported the results (data not shown).

Table 3 Models for Stroke which include interaction neuroticism (median split) by depression*.

	No cardiac disease			Cardiac disease		
	HR	[95% CI]	*P* value	HR	[95% CI]	*P* value
Model 1:						
• CESD score	1.12	[1.03 – 1.22]	.008	0.97	[0.79 – 1.20]	.776
• Neuroticism	1.06	[0.57 – 1.98]	.854	0.74	[0.23 – 2.44]	.625
• CESD by Neuroticism	0.94	[0.89 – 0.99]	.028	1.05	[0.94 – 1.17]	.440
Model 2:						
• CESD score ≥16	42.6	[5.23 – 347]	<.001	0.37	[0.01 – 26.3]	.649
• Neuroticism	0.85	[0.54 – 1.35	.484	1.04	[0.43 – 2.48]	.936
• CESD by Neuroticism	0.12	[0.03 - 0.45]	.002	2.60	[0.27 – 25.2]	.408

* Adjusted for age, sex, cognitive functioning, smoking, obesity, diabetes mellitus, functional limitations and hypertension.
Abbrevations: CESD, Center for Epidemiologic Studies Depression scale.

Figure 1 Absolute stroke rates per 1000 person years by depression and neuroticism status in patients with no cardiac history (n=1649).



Discussion

Main findings

In older persons without pre-existent cardiac disease, depression only predicts the onset of stroke over a 9-year follow-up in case of low neuroticism scores. Although we did not directly measure the level of subclinical vascular disease with imaging techniques, this finding may be explained by the presence of subclinical cardio- as well as cerebrovascular disease for the following reasons. Atherosclerosis generally develops over years, with the ultimate outcome of a cardiac or cerebrovascular event (Ross et al, 1993). Nonetheless, subclinical vascular disease is also associated with (specific) depressive symptoms (Bus et al, 2011). In case atherosclerosis first gives rise to an increased depressive symptom score, depression will emerge as a predictor for stroke in observational cohort studies. How does this theory fit with our results? First, our finding that depression increases the risk for stroke in patients with cardiac disease is in line with the theory that depressive symptoms in this population partly reflect the severity of underlying subclinical vascular disease (Ormel et al, 2011; de Jonge et al, 2012). In people without pre-existing cardiac disease, neuroticism may be assumed to be the most important pathway to depression (so called neurotic-depression) (Marijnissen et al, 2014). Nonetheless, in this group, several persons do have low neuroticism scores that by definition cannot have contributed to their depression. In this group, depressive symptoms may be a sign (or epiphenomenon) of subclinical vascular disease. Indeed, this hypothesis fits with our finding that depression in the presence of low neuroticism scores predicts the onset of stroke in these persons without manifest cardiac disease.

The interplay between neuroticism, vascular disease and depression is complex. Cross-sectional studies show that the association between depression and neuroticism is weaker in patients with vascular disease (Wouts et al, 2011; Marijnissen et al, 2014). Prospective studies studying the effect of neuroticism and depression on the incidence of stroke in concert are lacking. Nonetheless, some studies suggest that high levels of neuroticism may increase risk on vascular events. In the Swedish Twin Register, neuroticism predicted the development of coronary heart disease over 25 years of follow-up, but significance was lost after controlling for familial influences (Charles et al, 2008). In the UK Health and Lifestyle Survey, neuroticism predicted cardiac mortality, but not death from stroke (Shipley et al, 2007). In the Chicago Health and Aging Project, a psychosocial composite score including items of neuroticism was associated with an increased risk on stroke over and above the classical vascular risk factors for stroke

(Henderson et al, 2013). As this composite score also included items of depression, perceived stress and life dissatisfaction, the net effect of neuroticism remains unknown. In summary, it is most likely that neuroticism by itself is not related to vascular health, as was found in our study.

Methodological considerations

Three limitations should be taken into account. First, there was a selective dropout at baseline, as persons with missing neuroticism scores were more depressed and more vascular comprised. This might have reduced the power of the results in the cardiac subgroup in which no differential impact of depression by neuroticism status could be demonstrated. Effects for the non-cardiac subgroup are difficult to estimate, but most likely, results are conservative.

Secondly, biological markers of physical diseases have not been measured extensively. Previous papers on LASA, however, have confirmed good validity and high accuracy of our interview and algorithms used to classify the presence or absence of disease states (Kriegsman et al, 1996; Bremmer et al, 2006). Nonetheless, many patients have asymptomatic atrial fibrillation in later life, which may have underestimated our prevalence of cardiac arrhythmias (Prystowsky et al, 2010).

Thirdly, the number of participants with a stroke within subgroups was rather low, especially in the subgroup of non-depressed, non-cardiac patients. Therefore, confirmation in other samples seems relevant in order to rule out chance findings. Nonetheless, our findings within subgroups categorised by depression (yes/no) and neuroticism (high/low) status, were confirmed by analyses using depressive symptoms and neuroticism dimensionally.

Clinical implications

Neuroticism and vascular disease are two major vulnerability factors in late-life depression (Steunenberg et al, 2007; Wouts et al, 2011; Taylor et al, 2013). Depressed patients with high levels of neuroticism are more likely to benefit from classical antidepressant treatment strategies, compared to depressed patients with higher level of vascular disease (Alexopoulos et al, 2004; Kohler et al, 2010). These latter patients are also at increased risk of future health events like stroke (Wouts et al, 2008) and might benefit from optimising vascular disease-management including lifestyle intervention like walking or running. Therefore, replication studies as well as randomised controlled studies on the surplus of vascular screening in non-neurotic depressed older patients without known vascular disease are warranted.

Final conclusion

In summary, the results of our study suggest that in depressed older persons without a history of clinically overt vascular disease, persons with a low level of neuroticism have a higher risk of developing stroke, compared to those with a high level of neuroticism. These results support the idea that neurotic depression is a different type of depression than depression associated with vascular disease. Moreover, late-life depression in the context of low neuroticism might be a marker of vascular depression. This can be explained by subclinical vascular disease, in line with previous findings of an association between measures of generalised atherosclerosis and depressive symptoms in the population (Bus et al, 2011).

References

Alexopoulos GS, Kiosses DN, Murphy C et al. (2004) Executive dysfunction, heart disease burden and remission of geriatric depression. *Neuropsychopharmacology;* 29 (120):2278-2284.

Beekman AT, Deeg DJ, van Tilburg T et al. (1995) Major and minor depression in later life: a study of prevalence and risk factors. *J Affect Disord;*36(1-2):65-75.

Beekman AT, Deeg DJ, Van Limbeek J et al. (1997) Criterion validity of the Center for Epidemiologic Studies Depression scale (CES-D): results from a community-based sample of older subjects in The Netherlands. *Psychol Med;* 27:231-235.

Beekman AT, Geerlings SW, Deeg DJ et al. (2002) The natural history of late-life depression: a 6-year prospective study in the community. *Arch Gen Psychiatry;* 59(7):605-611.

Berkman LF, Berkman CS, Kasl S et al. (1986) Depressive symptoms in relation to physical health and functioning in the elderly. *Am J Epidemiol;*124:372-388.

Bremmer MA, Hoogendijk WJ, Deeg DJ et al. (2006) Depression in older age is a risk factor for first ischemic cardiac events. *Am J Geriatr Psychiatry;* 14(6):523-530.

Bus BAA, Marijnissen RM, Holewijn S et al. (2011) Depressive symptom clusters are differentially associated with atherosclerotic disease. *Psychol Med;* 41:1419-1428.

Charles ST, Gatz M, Kato K, Pedersen NL. (2008) Physical health 25 years later: The predictive ability of neuroticism. *Health Psychology;* 27(3):369-378.

Chobanian AV, Bakris GL, Black HR et al. (2003) The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA;* 289(19):2560-2572.

Dickens C, McGown L, Percival C et al. (2008)New onset depression following myocardial infarction predicts cardiac mortality. *Psychosom Med;* 70:450-455.

Folstein MF, Folstein SE, McHugh PR. (1975) "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res;* 12(3):189-198.

Henderson KM, Clark CJ, Lewis TT et al. (2013) Psychosocial distress and stroke risk in older adults. *Stroke;* 44(2):367-372.

de Jonge P, van den Brink RHS, Spijkerman TA et al. (2006) Only incident depressive episodes after myocardial infarction are associated with new cardiovascular events. *J Am Coll Cardiol;* 48(11):2204-2208.

de Jonge P &Roest AM. (2012) Depression and cardiovascular disease; the end of simple models. *BJP;* 201:337-338.

Köhler D, Thomas AJ, Lloyd A et al. (2010) White matter hyperintensities, cortisol levels, brain atrophy and continuing cognitive deficits in late-llife depression. *Br J Psychiatry;* 196:143-149.

Kohler S, Verhey F, Weyereer S et al. (2013) Depression, non-fatal stroke and all-cause mortality in old age: a prospective cohort study of primary care patient. *J Affect Disorders;*150(1):63-9.

van der Kooy K, van Hout H, Marwijk H et al. (2007)Depression and the risk for cardiovascular diseases: systematic review and meta analysis. *Int J Geriatr Psychiatry;* 22(7):613-26.

Kriegsman DM, Penninx BW, van Eijk JT et al. (1996) Self-reports and general practitioner information on the presence of chronic diseases in community dwelling elderly. A study on the accuracy of patients' self-reports and on determinants of inaccuracy. *J Clin Epidemiol;* 49(12):1407-1417.

Luteijn F, Starren J, van Dijk H. (2000) Herziene Handleiding bij de NPV [Revised manual Dutch personality questionnaire]. Lisse: Swets & Zeitlinger.

Marijnissen RM, Bus BAA, Schoevers RA et al. (2014) Atherosclerosis decreases the impact of neuroticism in late-life depression: Hypothesis of vascular apathy. *Am J Geriatr Psychiatry;* 22(8):801-10.

Ogden CL, Yanovski SZ, Carroll MD et al. (2007) The epidemiology of obesity. *Gastroenterology;* 132(6):2087-2102.

Ormel J & de Jonge P. (2011) Unipolar depression and the progression of coronary artery disease: toward an integrative model. *Psychother Psychosom;* 80:264-274.

Pan A, Sun Q, Okereke OI et al. (2011) Depression and risk of stroke morbidity and mortality: A meta-analysis and systematic review. *JAMA;* 306(11):1241-1249.

Prystowsky EN, Camm J, Lip GY et al. (2010) The impact of new and emerging clinical data on treatment strategies for atrial fibrillation. *J Cardiovasc Electrophysiol;* 21(8):946-958.

Ross. (1993) The pathogenesis of atherosclerosis: a perspective for the 1990s. *Nature;* 362: 801-809.

Shipley BA, Weiss A, Der G et al. (2007) Neuroticism, extraversion, and mortality in the UK Health and Lifestyle Survey: A 21-years prospective cohort study. *Psychosom Med;* 69:923-931.

Smits CHM, Deeg DJH, Bosscher R. (1995) Well-being and control in older persons: The prediction of well-being from control measures. *Int J Aging Hum Dev;* 40(3):237-250.

Sneed JR, Rindskopf D, Steffens DC et al. (2008) The vascular depression subtype: evidence of internal validity. *Biol Psychiatry;* 64:491-497.

Spijkerman T, de Jonge P, van den Brink RH et al. (2005) Depression following myocardial infarction: first-ever versus ongoing and recurrent episodes. *Gen Hosp Psychiatry;* 27:411-417.

Steunenberg B, Beekman ATF, Deeg DJH et al. (2003) Neuroticism in the elderly: The utility of the shortened DPQ-scales. *Tijdschrift voor Gerontologie en Geriatrie;* 34 (3):118-124.

Steunenberg B, Beekman AT, Deeg et al. (2006) Personality and the onset of depression in late life. *J Affect Disord*; 92(2-3): 243-251.

Steunenberg B, Beekman ATF, Deeg DJH et al. (2007) Mastery and neuroticism predict recovery of depression in later life. *Am J Geriatr Psychiatry;* 15:234-242.

Taylor WD, Aizenstein HJ, Alexopoulos GS. (2013) The vascular depression hypothesis: mechanisms linking vascular disease with depression. *Mol Psychiatry;* 18(9):963-74.

Tellegen A. (1985) Structures of mood and personality and their relevance to assessing anxiety, with a emphasis on self-report. *In Anxiety and the Anxiety Disorders,* Tuma AH, Maser JD (eds). Erlbaum: Hillsdale, NJ; 681-706.

Valkanova V and Ebmeier KP. (2013) Vascular risk factors and depression in later life: A systematic

review and meta-analysis. *Biol Psychiatry;* 73:406-413

Van Sonsbeek JLA. (1988) Methodological and substantial aspects of the OECD indicator of chronic functional limitations. *Maandbericht Gezondheid* (CBS); 88:4-17.

Watson D, Clark LA. (1984) Negative affectivty: the disposition to experience aversive emotional status states. *Psychol Bull;* 96:465-490.

Wouts L, Oude Voshaar RC, Bremmer MA et al. (2008) Cardiac disease, depressive symptoms and incident stroke in an elderly population. *Arch Gen Psychiatry;* 65(5):596-602.

Wouts L, Janzing JG, Lampe IK et al. (2011) The interaction between cerebrovascular risk factors and neuroticism in late-life depression. *Int J Geriatr Psychiatry;* 26(7):702-710.

CHAPTER 8

Summary and general discussion

Introduction

The main aim of this thesis was to study the association between subclinical vascular disease and late-life depression, taking into account different depressive symptom clusters and the interplay with neuroticism. In part one we focused on the association between depression and metabolic syndrome as a major risk factor for vascular disease. In part two we focused on the association between depression and the severity of atherosclerosis as a direct marker of subclinical vascular disease. In this second part, we also examined the interplay between subclinical vascular disease and neuroticism as a second (and more traditional) risk factor for depression.
The studies described in this thesis were mainly conducted in population-based samples of middle-aged and older persons, i.e. the Nijmegen Biomedical Study (chapter 2, 3, 5 and 6) and the Longitudinal Aging Study Amsterdam (chapter 7), with the exception of one study in the Netherlands Study of Depression in Older persons (NESDO), including 378 older persons suffering from a depressive disorder according to DSM-IV-TR criteria (chapter 4). This thesis illustrates the complexities of late-life depression. First, allowing for different depressive symptom profiles, i.e. the actual phenotypic expression. Secondly, by examining the interplay between a major psychological risk factor, i.e. neuroticism, and biological risk factors, i.e. subclinical vascular disease. Finally, by pointing to discrepancies between population-based and clinical samples. The following paragraphs will summarise the findings in the different chapters of this thesis, leading to a general discussion in which overall conclusions will be made and methodological considerations will be identified. Finally, after going back to the consequences of this thesis for the case reports, further implications for clinical practice and recommendations for future studies will be described.

Depressive symptom profiles and the metabolic syndrome

Several studies have found an association between depression and the metabolic syndrome (Koponen et al, 2008; Akbaraly et al, 2011; Pan et al, 2012) as well as with obesity assessed by Body Mass Index (BMI) (de Wit et al, 2010; Luppino et al, 2010). In chapter 2 and 3 we extended these findings by examining specifically the association between depressive symptom profiles and the metabolic syndrome and different measures of obesity (not only BMI but also Waist Circumference and Waist-Hip-Ratio). These studies were conducted within a population based sample aged 50 through 70 years participating in the Nijmegen Biomedical Study (NBS).

In chapter 2 we showed that depressive symptoms (BDI sum score) are significantly associated with the presence of the metabolic syndrome and show even stronger associations with the number of metabolic risk factors. The association between metabolic syndrome and depressive symptoms was primarily driven by the somatic-affective symptom-cluster of depression. Exploring sex-differences, we found that in men waist circumference, triglycerides and HDL cholesterol explained the variance in depressive symptoms whereas in women this effect was confined to waist circumference. Although pathophysiological mechanisms underlying the association between metabolic disturbance and depression remains to be elucidated, future studies should take into account possible sex-differences as well as the specific phenotype of depression that is associated with metabolic disturbances.

Depressive symptom profiles, late-life depressive disorder and obesity

In chapter 3 we explored the association between obesity and depression in more depth. Meta-analyses have found a reciprocal association between body mass index (BMI) and depression (de Wit et al, 2010; Luppino et al, 2010). We found waist circumference as the central component of the metabolic syndrome in the association between the metabolic syndrome and depression. Previous studies on these associations, however, did not take into account different symptom profiles as well as different definitions of obesity.
In line with earlier findings, we showed in chapter 3 the U-shaped relationship between Body Mass Index (BMI) and depressive symptoms. Excluding underweight patients, a positive correlation was found between BMI and all different measures of depressive symptoms e.g. BDI sumscore and the cognitive- and somatic-affective symptom clusters. These findings suggest that depressive symptoms in individuals with obesity may be affected by both psychological as well as physical pathways (Struijs et al, 2013). Measures of visceral obesity, however, were specifically associated with the somatic-affective symptom cluster (resp. waist circumference and Waist Hip Ratio). So visceral obesity, which is more indicative of vascular risk than BMI, is specifically associated with somatic-affective depressive symptoms. This finding might suggest that these symptoms are primarily due to a (subclinical) somatic condition.
Although the differences between men and women were not statistically different, post hoc analyses showed larger effect sizes for women than for men in all depressive symptoms measures in relation to BMI and WC. Sex differences may also occur because women are more likely to be stigmatized for being overweight or obese than are men.

In chapter 4 we examined whether the association found in a population based sample could be replicated in a clinically depressed sample aged 60 years and over who participated in the Netherlands Study of Depression in Older persons (NESDO) (Comijs et al, 2011). We showed that depressed older patients had a significantly lower waist circumference compared to non-depressed controls. It is concluded that the population-based findings on the positive association between obesity and depressive symptoms cannot be generalised to patients suffering from a late-life depression. Multiple linear regression analyses within the depressed group showed that both depression severity (Inventory of Depressive Symptoms) and duration-related depression characteristics (age of onset, duration of illness, life-time comorbid dysthymia) were associated with the waist circumference. Only the severity of depressive symptoms remained significant after further adjustment for the body mass index. When looking specifically at symptom profiles, the motivation subscale became significant.

Visceral adipose tissue is metabolically active by secretion of cytokine-family proteins, collectively called adipokines (Trujillo and Scherer, 2006, Milaneshi et al, 2012, Zhao and Stephens, 2013). These adipokines are hypothesized to induce a chronic low-grade inflammatory environment, thus contributing to the negative health effect of obesity. Some adipokines like leptin, resistin and adiponectin have been linked to mood regulation (Wilhelm et al, 2012; Milaneshi et al, 2102). In chapter 2 we found that adiponectin neither mediated nor moderated any of the associations found between depressive symptoms, the metabolic syndrome or the individual components of the metabolic syndrome e.g. waist circumference. In chapter 4 we found that a recently discovered adipokine, Neutrophil Gelatinase-Associated Lipocalin (NGAL), was associated with late-life depression, but only in the subgroup of patients with a pathologically increased waist circumference. These findings indeed link the metabolic activity of visceral adiposity to depressive symptoms, but findings on adiponectin show that there may be specific associations (and function) of different adipokines.

Depressive symptoms profiles, atherosclerosis and neuroticism

The association of depressive symptoms with vascular disease has primarily been examined in studies looking at clinically manifest vascular disease like cardiac patients or stroke. As manifest vascular disease is the result of a life-long accumulation of vascular burden, we examined in chapter 5 whether depression and depressive symptom profiles were also associated with the severity of atherosclerosis. This study was also

conducted within a population based sample aged 50 through 70 years participating in the Nijmegen Biomedical Study (NBS). Generalized atherosclerotic disease can be reliably measured by the intima media thickness (IMT) of the carotid artery and has been associated consistently with a negative cardiovascular outcome (Bots et al, 1996, 1997). We found a significant association between the depressive symptoms (BDI sum-score) and subclinical atherosclerosis as measured by the Intima Media Thickness, both in patients with and without coronary artery disease. So the relationship seems to be specific for atherosclerotic disease independent of vascular events. Furthermore, the positive association between depressive symptoms and atherosclerosis is primarily driven by the somatic-affective symptom cluster of depression.

So, in middle-aged and older people in the general population, the association between depressive symptoms and subclinical atherosclerotic disease, visceral obesity and the metabolic syndrome could be explained by the somatic-affective symptom cluster within the depression symptomatology. This might suggest that these symptoms are primarily due to a (subclinical) somatic condition (Meijer et al, 2013) . Subclinical vascular disease and the risk factors obesity and the metabolic syndrome in general might inflate depressive symptoms scores and may explain why treatment of depression in for example cardiac patients hardly effect vascular outcome (Glassman et al, 2002; Berkman et al, 2003; van Melle et al, 2007; Lespérance et al, 2007).

Subsequently, we were interested whether and how subclinical vascular disease would interact with another major risk factor for late-life depression, neuroticism, in explaining variance in these depressive symptom profiles. Based on two previous studies (Oldehinkel et al, 2003; Wouts et al, 2011), we expected that neuroticism and subclinical atherosclerotic disease as measured by Intima Media Thickness would negatively interact with regard to the presence of depressive symptoms.
In chapter 6 we described that in our study neuroticism was associated with the total number of depressive symptoms and with both cognitive-affective and somatic-affective symptoms. The strength of this association was much larger than the association with subclinical as well as clinical vascular disease. Therefore, it is remarkably that neuroticism has been largely neglected in the field of late-life depression. We found a negative interaction between neuroticism and atherosclerosis in explaining variance of the cognitive-affective symptoms of depression, but not the somatic-affective symptoms. The effect of neuroticism in explaining depressive symptoms diminishes in the presence of more severe atherosclerosis. This may be explained by apathy due to cerebrovascular disease and fits the hypothesis of vascular apathy (see chapter 6).

Low neuroticism as a marker for subclinical vascular disease in late-life depression

Finally, based on previous findings in this thesis, we postulated in chapter 7 that the association between depression and vascular events is confounded by underlying vascular disease in later life and that this may differ for different subtypes of depression (vascular versus neurotic-associated depression). We expected that vascular depression, defined theoretically by a high aetiological contribution of vascular disease, increases the risk on future strokes, whereas neuroticism-associated depression does not.
Previously, it had been shown that depression only predicted stroke in cardiac patients, but not in non-cardiac patients. Using the same dataset of the Longitudinal Aging Study Amsterdam (LASA), a population-based cohort study with 9-year follow-up (≥ 55 years), we showed that in non-cardiac patients, depression still predicted incident stroke in those with low neuroticism, but not in those with high neuroticism. The balance between the two different vulnerability factors in late-life depression, neuroticism and (subclinical) vascular disease might be important profiling factors that give an indication of depressive subtype and possible treatment outcome. First results of some small randomised controlled trials, indeed point to better outcome when treatment is focused more specifically on these underlying mechanisms (e.g. Arean et al, 2010).

Overall conclusions

As stated in chapter 1, the main aim of this thesis was to study the association between the late-life depression and subclinical vascular disease, taking into account different depressive symptom clusters and neuroticism. We can conclude that subclinical vascular disease is associated with depressive symptoms in later life. More specifically, depressive symptoms in later life are associated with the metabolic syndrome, obesity and generalised atherosclerosis (hypothesis 1). These associations may in part be explained by increased levels of adipokines, although these associations do not seem consistent for the different adipokines. Furthermore, the somatic-affective symptom cluster of the Beck Depression Inventory drives these associations. Finally, we show the relevance of studying subclinical vascular disease and neuroticism in concert as two different etiological pathways in late-life depression. On the one hand, neuroticism explains less variance in depressive symptoms in the presence of subclinical vascular disease. On the other hand, depression in the absence of neuroticism is suggestive of clinically relevant subclinical vascular disease (hypothesis 2).

Collectively, these studies show the complexity and heterogeneous nature of late-life depression. More attention for specific symptom profiles, as well as the (interplay between the) two major pathways towards late-life depression, may guide clinical decision making, although firm conclusion should be addressed in prospective cohort studies and clinical trials.

Methodological considerations

Study type

Five of the six studies described in this thesis are based on cross-sectional findings. This limits causal interpretation, as it can not be determined which of the factors occurred first. Still to date no prospective studies are available relating depressive symptom clusters to obesity, metabolic syndrome, subclinical vascular disease and neuroticism in later life.

Depressive symptoms versus (major) depressive disorder

Only one study was confined to a clinical sample of depressed older adults (chapter 4), whereas the five other studies were conducted in population-based samples. In population-based samples, bias toward the healthiest people may have occurred resulting in a lower severity of depressive symptoms as well as a lower severity of atherosclerosis. This may have resulted in less overall variance of the atherosclerosis and depressive symptoms as well as the probability that both characteristics could explain each other.

Depressive symptoms are generally considered on a continuum with depressive disorder, but it is not clear whether this assumption really holds true (Hetrick et al, 2008). Scores on Beck Depression Inventory, as used in this thesis, may reflect common somatic experiences to a certain degree. Many people report symptoms of fatigue or loss of libido, regardless of their medical status. The relative effect of these non-specific symptoms on the overall depressive score is more prominent among people with low levels of depressive symptoms (Thombs et al, 2010). Lower levels of depressive symptoms in the population, as found in the Nijmegen Biomedical Study, might thus be confounded by underlying somatic illnesses (Thombs et al, 2010). Nonetheless, post acute myocardial infarction patients did not have higher somatic symptom scores than psychiatry out-patients and reported, on average, somatic symptom scores only one point higher than under graduate students. (Thombs et al, 2010). Furthermore, 16.7% of the participants in the Nijmegen Biomedical Study scored above the cut-off of 10 on the BDI-I, which is indicative of mild depressive symptoms (Pizzi et al, 2008).

Somatic-affective symptoms: subtype of depression or epiphenomenon of vascular disease
The factor structure of the Beck Depression Inventory (BDI) was used to discriminate between cognitive-affective symptoms and somatic-affective symptoms. As pointed out above, low scores on the BDI may point to non-specific symptoms and this may be especially true for the somatic-affective symptoms (Thombs et al, 2010). Therefore, we cannot exclude the possibility that the association of somatic-affective depressive symptoms with atherosclerosis, obesity and the metabolic syndrome simply reflects underlying somatic illnesses. Nonetheless, also in cardiac patients suffering from a major depressive disorder, only the somatic-affective symptom cluster predicted a negative cardiac prognosis (adjusted for the severity of the heart condition at baseline) (e.g. de Jonge et al, 2006). Furthermore, in older persons suffering from late-life depression, those with significant vascular risk factors indeed had more somatic-affective symptoms compared to depressed older persons without vascular risk factors (Naarding et al, 2007). Having said this, we still cannot be sure that the pathogenesis of somatic-affective symptoms is similar for depressed cardiac patients and depressed non-cardiac patients. This issue deserves more attention in future studies.
In our sample of depressed older adults (chapter 4), the severity of depression was measured with the Inventory of Depressive Symptoms self-report (IDS-SR) (Rush et al, 1996). The IDS, however, has three different dimensions, namely a mood, motivation and somatic dimension (Hegeman et al, 2012). It should be noted that the somatic dimension, however, only include two symptoms. The motivation sub scale was most comparable to the somatic-affective symptom profile of the BDI. Interestingly, the waist circumference was associated with both sum score of the Inventory of Depressive Symptoms (IDS) and the motivation subscale of the IDS (see chapter 4). These findings collectively are in line with a somatic-affective subtype of major depressive disorder.

Atherosclerotic disease
Current hypotheses on the impact of vascular disease on mood regulation include several pathways. Recently, a model has been described that integrates disconnection, inflammation and hypoperfusion processes as causal pathways to vascular depression (Taylor et al, 2013). Vascular disease may contribute to altered brain function characteristic of depression (dorsal hypometabolism, ventral hypermetabolism) either through structural damage adversely affecting connectivity, through perfusion deficits altering regional function, or both. Pro-inflammatory processes increase vascular risk, but may also affect brain function through independent processes. Although we did not assess brain functioning but looked at markers of metabolic risk and generalized atherosclerosis, these conditions probably affect mood regulation by inducing a pro-inflammatory state or by structural damage to mood regulation circuitries of the brain. Nonetheless, none

of these (mediating) pathways have been studied directly. We assessed the Intima Media Thickness (IMT) as a marker for generalized atherosclerosis. It is assumed that the IMT in the common carotid arteries is associated with cerebrovascular disease (Cao et al, 2003). However by including neuroimaging parameters we might have been able to discern between direct effects of atherosclerosis on mood regulation and peripheral effects of atherosclerosis that result in more non-specific symptoms that may overlap with depression, like vital exhaustion and fatigue due to a diminished physical condition.

Obesity

Although we have used, beside the Body Mass Index, the most convenient anthropometric indices of visceral adipose tissue (Waist circumference and Waist-to-Hip Ratio) in older people (Villareal et al, 2005), of course Computed Tomography at the level of the fourth lumbar vertebra is the gold standard for quantification of visceral fat (Weber-Hamann et al, 2006). However, anthropometric measures still provide adequate estimates of abdominal fatness and its distribution in men and women aged 55 to 70 years (Stewart et al, 2003). The amount of abdominal fat as assessed by magnetic resonance imaging (MRI) was highly correlated with the waist circumference (for men r=.60, for women r=.72) and the waist to hip ratio (for men r= 0.71, for women r=.54), whereas the BMI was most strongly associated with overall subcutaneous body fat (for men r=.70, for women r=86) (Stewart et al, 2003).

Visceral fat tissue is metabolically active by the secretion of both pro-and anti-inflammatory cytokines, collectively called adipokines (Trujillo and Scherer, 2006; Milaneshi et al, 2012; Zhao & Stehens, 2013). How these adipokines interact with each other and which adipokines might be specifically linked to depression remains to be elucidated. In our study, we only confirmed an association with NGAL, but not adiponectin. At first, we had chosen to explore the role of adiponectin. In contrast to other adipokines, adiponectin expression is a protective cytokine for vascular health (Matsuzamwa et al, 2011) and several studies have linked adiponectin to depressive symptoms (Wilhelm et al, 2012). Nonetheless, we could not confirm these previous findings. Secondly, we looked at plasma levels of NGAL. This was done because NGAL levels were found to be increased in depressed compared to non-depressed older people (Naudé et al, 2013), animal research offer a biologically plausible explanation for this link (Wang et al, 2007) and finally, NGAL has been identified as an adipokine. Our results, however, should definitively be replicated, preferably in studies testing blood levels and expression in adipocytes of the whole array of adipokines.

Metabolic syndrome
In our study the Metabolic Syndrome (MetS) was defined according to the International Diabetes Federation (IDF) (www.idf.org/webdata/docs/IDF-Meta_def_final.pdf, 2006) as the presence of central obesity (defined as waist circumference with ethnicity specific values; if BMI is > 30 kg/m2 central obesity can be assumed and waist circumference does not need to be measured) plus any two of the following four factors: (1) Raised triglycerides (≥150 mg/dL (1.7 mmol/L) or specific treatment for this lipid abnormality, (2) reduced HDL cholesterol (<40 mg/dL (1.03 mmol/L) in males and <50 mg/dL (1.29 mmol/L) in females or specific treatment for this lipid abnormality, (3) Raised blood pressure (systolic BP ≥130 or diastolic BP ≥85 mm Hg or treatment of previously diagnosed hypertension), (4) Raised fasting plasma glucose FPG ≥100 mg/dL (5.6 mmol/L) or previously diagnosed type 2 diabetes.

Another widely used definition of the Metabolic Syndrome is according to the National Cholesterol Education Program Adult Treatment Panel III guidelines as having 3 or more of the following criteria: (1) waist circumference > 102 cm in men or > 88 cm in women; (2) triglyceride level ≥ 150 mg/dL; (3) high-density lipoprotein cholesterol < 40 mg/dL in men or < 50 mg/dL in women; (4) systolic/diastolic blood pressure ≥ 130/85 mm Hg and/or currently using antihypertensive medication; and (5) fasting glucose ≥ 110 mg/dL and/or currently using antidiabetic medication (NCEP, 2002).

The most important difference between the IDF definition and the NCEP definition is that central obesity is mandatory in the IDF definition. On the one hand, this may have strengthened the findings in our studies, since abdominal obesity appears to be the most important component.
Furthermore the cut off of HDL cholesterol for men is lower in the IDF definition (<20 mg/dL vs < 40 mg/dL in NCEP) and the cut off for the fasting glucose is lower (≥100 mg/dL vs ≥ 110 mg/dL in NCEP). Nonetheless, we also looked at the other components of the metabolic syndrome at a dimensional level, thereby overcoming problems due to (arbitrarily) cut-offs of the individual criteria.

Neuroticism
In chapter 6, neuroticism was measured using the Dutch version of the revised Eysenck Personality Questionnaire (EPQ-RSS) (Eysenck & Eysenck, 1975; Eysenck et al, 1985). In chapter 7, neuroticism was measured with the Dutch Personality Questionnaire (DPQ) (Luteijn et al, 1975). Both questionnaires, however, have not been developed for older people and robust cross-validation studies in this age-group are lacking.
In the Longitudinal Aging Study Amsterdam, neuroticism was operationalized by using

a subset of 25 items out of a list of 36 neuroticism items from the Dutch Personality Questionnaire (DPQ; Luteijn, Starren, & van Dijk, 1975, 2000), because the original DPQ scale contained items that were less valid for an aging population and contained too many items for administration in older populations (de Beurs et al, 2000; Smits et al, 1995; Steunenberg et al, 2003). This shortened scale appeared to be a reliable (Cronbach's a .86) and valid instrument to measure neuroticism in the elderly population (Steunenberg et al, 2003). Total scores range between 0 and 50 and these DPQ items have strong negative relations with the Emotional Stability scale of the Revised NEO Personality Inventory (NEO-PI-R; Luteijn et al, 2000). Moreover, the reliability and stability of neuroticism as measured with the NEO-FFI is good in an older population (Hoekstra et al, 1996).
The EPQ contains items that are less applicable to older persons, like "Would it be interesting for you to use drugs?" and "Do you become irritated by people who drive cautiously?", as well as items that might be more closely relate to other constructs in later-life, like "Do you often feel lonely?" or "Do you have many friends?". Nonetheless, a recent study with a follow-up of 37 years in women showed that neuroticism as measured with the Eysenck Personality Questionnaire was relatively stable from mid-life to old-age (Billstedt et al, 2014).
Altogether, these data suggest that neuroticism is a relatively stable construct over the life-span, which can be measured sufficiently reliably in later life (Lucas & Donnellan, 2011) and is not affected by physical health variables (Steunenberg et al, 2005).

A second methodological issue is that we measured neuroticism and depressive symptoms at the same time. The presence of depression amplifies the personality profile of people prone to depression (Costa et al, 2005). However, the relationship between change in personality and change in depressive symptoms is at most moderate (Santor et al, 1997; Marijnissen G et al, 2002; Costa et al, 2005), suggesting that these are not similar constructs.

Apathy
Unfortunately, apathy was not directly measured and the relationship between cognitive-affective symptoms of depression and apathy has not been studied in this thesis. It is conceivable that apathy is associated with indifference and lower cognitive activity like rumination, worrying or suicidal thoughts. Nonetheless, the absence of cognitive-affective symptoms is only part of the apathy syndrome (Robert et al, 2009). Apathy as a disorder of motivation that persists over time is defined by consensus and should meet the following requirements: (1) the core feature of apathy, diminished motivation, must be present for at least four weeks, (2) two of the three dimensions of apathy

(reduced goal-directed behavior, goal-directed cognitive activity, and emotions) must also be present, (3) there should be identifiable functional impairments attributable to the apathy. Finally, exclusion criteria are specified to exclude symptoms and states that mimic apathy (Robert et al, 2009). Our hypothesis of vascular apathy is based only on one component of apathy namely the reduced cognitive activity. Therefore, we cannot exclude the possibility that reduced cognitive activity is discriminative between apathy and depression or just simply reflects their phenomenological overlap.

Implications for clinical practice

When translating our results to clinical care, we must acknowledge that most of the results in this thesis are from cross-sectional studies. The cross-sectional design of the studies does not allow our results to be interpreted causally. Therefore, our findings can not directly be applied in clinical decision making as if they were derived from randomised controlled trials. Still, hopefully, these results will bring the importance of vascular risk factors and subclinical vascular disease into the awareness of clinicians in order to shape or refine their decisions.

In the general population subclinical atherosclerosis and the risk factors visceral obesity and the metabolic syndrome in general may inflate depressive symptoms scores. It may even lead to misdiagnosis of depression in some cardiac patients due to the presence of somatic-affective symptoms that reflect the severity of the atherosclerotic disease but are not part of a formal depressive syndrome, as is implicitly stated by de Jonge and Roest (de Jonge & Roest, 2012).
This could argue for adaptations of the criteria for depressive disorder in patients with atherosclerosis, visceral obesity and the metabolic syndrome with less emphasis on somatic-affective symptoms.
From a clinical point of view, we could argue to differentiate it as a subtype of late-life depression, with specific underlying etiological pathways. Patients suffering from this subtype of depression may benefit from optimising vascular disease-management and treatment programs including physical exercise program like walking or running because this enhances muscle and skeletal strength, decreases obesity and positively affects depression. The other way around, because depression is associated with poorer adherence, interventions for medical problems in patients with atherosclerosis, obesity and metabolic syndrome might benefit from effective concurrent treatment of depression. Altogether, this argues for collaborative care by old-age psychiatrists and specialists in geriatric, internal or vascular medicine.

Back to the case-reports

What can we learn from our studies with respect to the case-reports presented in the general introduction of this thesis? In general, we can conclude that it seems important (but difficult) to differentiate between somatic-affective symptoms, features of sickness behaviour (generally thought to be induced by inflammatory processes) and apathy. Somatic-affective symptoms may point to underlying somatic conditions but may also indicate a depressive disorder. Furthermore, neuroticism and vascular disease should be explicitly evaluated and estimated on the presumed contribution to depressive symptoms in an individual patient. Hereby, it is important to realize that the association between neuroticism and depression may be reduced in the presence of atherosclerosis as well as that the absence of neuroticism increases the risk of clinically relevant subclinical vascular disease.

Mr A, a 68-year-old man, with a history of a late-onset depression three years ago, was presented by the neurologist after a non-fatal stroke with depressive symptoms and inactivity. The main question was whether there was a recurrence of a depressive episode. Probably the occurrence of the first depression was the first marker of his vascular disease burden, as the diagnostic workup showed a serious degree of subclinical atherosclerosis even without clinical vascular disease in history. Retrospectively, the low level of neuroticism of mr A as well as the first depression at the age of 65 years, would have justified a vascular check-up three years ago.

Mrs B, a 70-year-old woman, who was admitted at the emergency ward of old-age psychiatry with the diagnosis of recurrence of depression. This time, unfortunately, without precipitating event and no recovery after optimising the therapy that had been successful in the past. The main question was how we could explain this depressive episode without precipitating event and without response to treatment. We may postulate that cerebrovascular atherosclerosis had lead to frontostriatal dysfunction and neuropsychological deficits (especially decreased processing speed and executive dysfunctioning). The family of Mrs B already noticed that in the last decade she was less worrisome and anxious. The impact of neuroticism in explaining the late-life depressive symptoms has attenuated. This might be an explanation for occurrence of the depressive episode, more symptoms of apathy, the absence of a precipitating event, and finally, treatment resistance for previously successful treatment strategies.

Mr C, a 55-year-old man, was referred because of depression with prominent symptoms

of fatigue, inactivity, less social involvement and slowness in thinking. The somatic history reported Diabetes Mellitus type 2 and hypertension. On physical examination, we found both hypertension and a pathologically increased waist circumference (125 cm). The main question was whether Mr C was suffering from a late-life depression. Although difficult to differentiate from apathy, Mr C was most likely suffering from a subtype of depression with predominant somatic-affective symptoms and/or a "metabolic depression". Especially in this type of patients, we would suggest to augment traditional treatment of depression with lifestyle training, for example a physical exercise program in order to enhance muscle and skeletal strength and decrease obesity.

Finally miss D, a 84-year-old woman that was seen in a nursing home, refusing to cooperate in rehabilitation after a hip-fracture. She presented with a severe major depressive episode in later life, suffering from depressed mood, feelings of quilt, loss of appetite and underweight. Probably, we see a specific profile of depression in this frail older woman. She might have lost more weight due to comorbid physical frailty, which in itself is associated with depression. Or due to aging she developed some nutritional deficiencies that also have contributed to her depressive symptoms. The severity of her depressive episode and associated weight loss may be typical for depressed older adults presenting in routine psychiatric care, but, as shown in this thesis, may differ from those classified as depressed in population based samples. For these patients, multidisciplinary approach is essential for prioritizing the different problems and treatment components (physical rehabilitation, nutritional intervention, treatment of depression).

Recommendations for future studies

Most of the associations found were based on cross-sectional population based research. Acknowledging the age-specific effects we argue for further longitudinal studies specifically in depressed older persons. Such studies might be able to identify depressed subgroups with an unfavourable prognosis with respect to their physical health status. Future cohort studies, however, should be clearly focused in order to measure the most relevant concepts in sufficient detail. First, the whole array of adipokines should be tested as well as the relative impact of the waist circumference assessed with both anthropometric indices and abdominal MR imaging. Secondly, depression should be measured extensively, taking into account the different symptom dimensions of depression as well as other psychological concepts like anxiety, somatization and personality. These concepts should preferably be measured by both self-report scales as semi-structured psychiatric interviews administered by trained mental health professionals. Another

option is to enrich population based cohort studies with a clinical cohort of depressed older patients. Finally, the phenotypic expression of depression, vascular risk factors and peripheral measures of subclinical vascular health should be related to the mood regulating brain circuitries by including neuroimaging and more refined neuropsychological testing.

References

Akbaraly TN, Ancelin ML, Jaussent I et al. (2009) Metabolic syndrome and onset of depressive symptoms in the elderly. *Diabetes Care;* 34 (4):904-909.

Arean PA, Raue P, Mackin RS et al. (2010) Problem-solving therapy and supportive therapy in older adults with major depression and executive dysfunction. *Am J Psychiatry;* 167(11):1391-8.

Berkman LF, Blumenthal J, Burg M et al. (2003) Writing Committee for the ENRICHD Investigators. Effects of treating depression and low perceived social support on clinical events after myocardial infarction. The Enhancing Recovery In Coronary Heart Disease patients (ENRICHD) randomized trial. *JAMA;* 289:3106-16.

Beurs de E, Beekman ATF, Deeg DJH et al. (2000) Predictors of change over three years in anxiety-symptoms of older persons: results from the Longitudinal Aging Study Amsterdam. *Psychological Medicine;* 30:515–527.

Billstedt E, Skoog I, Dubertstein et al. (2014) A 37-year prospective study of neuroticism and extraversion in women followed from mid-life to late-life. *Acta psychiatry Scand;* 129: 35-43.

Bots ML, Hoes AW, Koudstaal PJ et al. (1997) Common carotid intima-media thickness and risk of stroke and myocardial infarction : the Rotterdam Study. *Circulation;* 96:1432-1437.

Bots ML, Hofman A, de Jong PT et al. (1996) Common carotid intima-media thickness as an indicator of atherosclerosis at other sites of the carotid artery. The Rotterdam Study. *Annals of Epidemiology;* 6:147–153.

Cao JJ, Thach C, Manolio TA, et al. (2003) C-reactive protein, carotid intima-media thickness, incidence of ischemic stroke in the elderly. The Cardiovascular Health Study. *Circulation;* 108: 166e170.

Comijs, HC, van Marwijk HW, van der Mast RC et al. (2011) The Netherlands study of depression in older persons (NESDO); a prospective cohort study. *BMC Researc Notes;* 4:524.

Costa PT Jr, Bagby RM, Herbst JH et al. (2005) Personality self-reports are concurrently reliable and valid during acute depressive episodes. *J Affect Disord;* 89(1-3):45-55.

Eysenck JH & Eysenck SBG (1975) Manual of the Eysenck Personality Questionnaire. London: Hodder and Stoughton.

Eysenck SBG, Eysenck HJ, Barrett P. (1985) A revised version of the Psychoticism Scale. *Person Individ Diff;* 6:21e29 P.

Glassman AH, O'Connor CM, Califf RM et al. (2002) Sertraline treatment of major depression in patients with acute MI or unstable angina. *JAMA;* 288:701-9.

Hegeman JM, Wardenaar KJ, Comijs HC et al. (2012) The subscale structure of the Inventory of Depressive Symptomatology Self Report (IDS-SR) in older persons. *Journal of Psychiatric Research;* 46:1383-1388.

Hetrick SE, Parker AG, Hickie IB et al. (2008) Early identification and intervention in depressive disorders: towards a clinical staging model. *Psychother Psychosom;* 77:263-270.

Hoekstra HA, Ormel J, Fruyt de F. (1996) Dutch Manual of NEO-PI-R & NEO-FFISwets & Zeitlinger, Lisse, the Netherlands.

IDF (2009) The IDF consensus worldwide definition of the metabolic syndrome www.idf.org/webdata/docs/IDF_Meta_def_final.pdf).

de Jonge P, Ormel J, van den Brink RH et al. (2006) Symptom dimensions of depression following myocardial infarction and their relationship with somatic health status and cardiovascular prognosis. *Am J Psychiatry;* 163(1):138-144.

de Jonge P and Roest A. (2010) Depression and cardiovascular disease: the end of simple models. *BJP;* 201:227-338.

Koponen H, Jokelainen J, Keinanen-Kiukaanniemi S et al. (2008) Metabolic syndrome predisposes to depressive symptoms: a population-based 7-year follow-up study. *J Clin Psychiatry;* 69(2):178-82.

Lespérance F, Frasure-Smith N, Koszycki D et al. (2007) Effects of citalopram and interpersonal psychotherapy on depression in patients with coronary artery disease. The Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE) Trial. *JAMA;* 297:367-79.

Lucas RE and Donnellan MB. (2011) Personality development across the life span: Longitudinal analyses with a national sample from Germany. *J of Personality and Social Psychology*; 101:847-861.

Luppino FS, deWit LM, Bouvy PF et al. (2010) Overweight, obesity and depression. A systemic review and meta-analysis of longitudinal studies. *Arch Gen Psych;* 67:220–229.

Luteijn F, Starren J, van Dijk H. (1975) Handleiding Bij de NPV. Swets & Zeitlinger, Lisse.

Luteijn F, Starren J, van Dijk H. (2000) Herziene Handleiding bij de NPV [Revised manual Dutch personality questionnaire]. Lisse: Swets & Zeitlinger.

Marijnissen G, Tuinier S, Sijben AES et al. (2002) The temperament and character inventory in major depression. *J Afffect Disord;* 70:219-223.

Matsuzamwa Y, Funahashi T, Nakamura T. (2011) The concept of metabolic syndrome; contribution of visceral fat accumulation and its molecular mechanism. *Journal of Atherosclerosis and Thrombosis;* 18:629-639.

Meijer A, Zuidersma M, de Jonge P. (2013) Depression as a non-causal variable risk marker in coronary heart disease. *BMC Med;* 11:130.

van Melle JP, de Jonge P, Honig A et al. (2007) Effects of antidepressant treatment following myocardial infarction. *Br J Psychiatry;* 190:460-6.

Milaneshi Y, Simonsick EM, Vogelzangs N et al. (2012) Leptin, abdominal obesity and onset of depression in older men and women. *J Clin Psychiatry;* 73(9):1205-1211.

Naarding P, Tiemeier H, Breteler MM et al. (2007) Clinically defined vascular depression in the general population. *Psychological Medicine;* 37:383-392.

Naudé PJW, Eisel ULM, Comijs HC et al. (2013). Neutrophil Gelatinase-Associated Lipocalin: A novel inflammatory marker associated with late-life depression. *J Psychosom Res;* 75 (5):444-450.

National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). (2012) Third

Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation;* 106(25):3143-3421.

Oldehinkel AJ, Ormel J, Brilman EI et al. (2003) Psychosocial and vascular risk factors of depression in later life. *J Affect Disord;* 74(3):237-246.

Pan A, Keum N, Okereke OI et al. (2012) Bidirectional association between depression and metabolic syndrome. *Diabetes;* 35:1171-1180.

Pizzi C, Manzoli L, Mancini S et al. (2008) Analysis of potential predictors of depression among coronary heart disease risk factors including heart rate variability, markers of inflammation, and endothelial function. *Eur Heart J;* 29:110–11.

Robert P, Onyike CU, Leentjens AF et al. (2009) Proposed diagnostic criteria for apathy in Alzheimer's disease and other neuropsychiatric disorders. *Eur Psychiatry;* 24:98e104.

Roger VL, Go AS, Lloyd-Jones D et al. (2012) Heart disease and stroke statistics-2012 update: a report from the American heart Association. *Circulation;* 24:e2-e220.

Rush AJ, Gullion CM, Basco MR et al. (1996) The Inventory of Depressive Symptomatology (IDS): psychometric properties. *Psychological Medicine;* 26(3):477-486.

Santor DA, Bagby RM, Joffe RT (1997) Evaluating stability and change in personality and depression. *J Pers Soc Psychol;* 73:1354e1362.

Smits CHM, Deeg DJH, Bosscher R. (1995) Well-being and control in older persons: the prediction of well-being from control measures. *The International Journal of Aging & Human Development;* 40:237–250.

Steunenberg B, Beekman ATF, Deeg DJH et al. (2003) Neuroticism in the elderly: the utility of the shortened DPQscales (in Dutch). *Tijdschrift voor Gerontologie en Geriatrie;* 34(3):118-124.

Steunenberg B, Twisk JW, Beekman AT et al. (2005) Stability and change of neuroticism in aging. *J Gerontol B Psychol Sci Soc Sci;* 60(1):27-33.

Stewart KJ, DeRegis JR, Turner KL et al. (2003) Usefulness of anthropometrics and dual-energy X-ray absorptiometry for estimating abdominal obesity measured by Magnetic Resonance Imaging in older men an women. *J of Cardiopulmonary Reh;* 23:109-114.

Struijs SY, Groenewold NA, Oude Voshaar RC et al. (2013) Cognitive vulnerability differentially predicts symptom dimension of depression. *J Affect Disord;* 151(1):92-9.

Taylor WD, Aizenstein HJ, Alexopoulos GS. (2013) The vascular depression hypothesis: mechanisms linking vascular disease with depression. *Mol Psychiatry;* 18(9):963-74.

Tiemeier H, van Dijck W, Hofman A et al. (2004) Relationship between atherosclerosis and late-life depression: the Rotterdam Study. *Arch Gen Psychiatry;* 61:369e376.

Thombs BD ,Ziegelsteig RC, Pilote L et al. (2010) Somatic symptom overlap in beck depressioninventory-IIscoresfollowingmyocardial infarcation. *Br J Psych;* 197:61-66.

Trujillo ME, Scherer PE. (2006) Adipose tissue-derived factors: impact on health and disease. *Endocrinve Rev;* 27 (7):762-77.

Villareal DT, Apovian CM, Kushner RF et al. (2005) American Society for Nutrition; NAASO, The Obesity Society. Obesity in older adults: Technical review and position statement of the American Society for Nutrition and NAASO, The Obesity Society. *Am J Clin Nutri;* 82:923-934.

Wang Y, Lam KSL, Kragen EW et al. (2007) Lipocalin-2 is an inflammatory marker closely associated with obesity, insulin resistance and hyperglycemia in humans. *Clin Chem;* 53(1):34-41.

Weber-Hamann B, Werner M, Hentschel F et al. (2006) Metabolic changes in elderly patients with major depression: Evidence for increased accumulation of visceral fat at follow-up. *Psychoneuroendocrinolog;* 31:347-354.

Wilhelm CJ, Choi D, Huckans M et al. (2012) Adipocytokine signaling is altered in flinders sensitive line rats, and adiponectin correlates in humans with some symptoms of depression. *Pharmacology, Biochemistry and Behavior;* 103(3):643-651.

Wit de L, Luppino F, van Straten A et al. (2010) Depression and obesity: a meta-analysis of community-based studies. *Psychiatry Research;* 178(2):230-5.

Wouts L, Janzing JG, Lampe IK, et al. (2011) The interaction between cerebrovascular disease and neuroticism in late-life depression: a cross-sectional study. *Int J Geriatr Psychiatry;* 26:702e710

Zhao P, Stephens J. (2013) STAT1, NF-kB and ERKs play a role in the induction of lipocalin-2 expression in adipocitytes. *Mol Metab;* 2:161-170.

Summary in Dutch | Samenvatting in het Nederlands

Introductie

Depressie op latere leeftijd heeft negatieve gevolgen zoals een hogere incidentie van verschillende lichamelijke ziekten, een verminderde kwaliteit van leven en verhoogd gebruik van de gezondheidszorg. Depressie is een heterogene aandoening voor wat betreft de fenomenologie en onderliggende pathofysiologische mechanismen. In dit proefschrift onderzochten we de heterogeniteit met betrekking tot symptoom profielen van depressie (somatisch-affectieve symptomen en cognitief-affectieve symptomen) in relatie tot twee belangrijke wegen die leiden tot een ouderdomsdepressie, namelijk (subklinische) vasculaire ziekte en de persoonlijkheidstrek neuroticisme. In het proefschrift zochten we naar antwoorden op de volgende vragen. Zijn depressieve symptomen ook geassocieerd met subklinische vasculaire ziekten, dus milde vormen van vaatlijden welke zich (nog) niet hebben gemanifesteerd met een hart- of hersen-infarct? Zijn depressieve symptomen, met name het somatisch-affectieve cluster, niet de symptomen van een onderliggende ziekte? Hoe zullen vaatziekten en neuroticisme elkaar beïnvloeden in het ontstaan van de ouderdomsdepressie? In hoofdstuk 1 werden een viertal gevalsbeschrijvingen gepresenteerd om de klinische relevantie van deze vragen te illustreren.

We formuleerden de volgende hypotheses:

1. Subklinische vasculaire ziekte is geassocieerd met ouderdomsdepressie.
    a. Het metabool syndroom, een clustering van risicofactoren voor hart- en vaat-ziekten, is geassocieerd met de ouderdomsdepressie.
    b. Obesitas is geassocieerd met de ouderdomsdepressie.
    c. Gegeneraliseerde atherosclerose (geïndexeerd door de dikte van de intima media (IMT) van de arteria carotis) is geassocieerd met de ouderdomsdepressie.
2. Subklinische vasculaire ziekte, meer specifiek het metabool syndroom, obesitas en gegeneraliseerde atherosclerose, zijn geassocieerd met het somatisch-affectieve symptoom cluster van de depressie.
3. Subklinische vasculaire ziekte en neuroticisme representeren twee verschillende pathofysiologische mechanismen van de ouderdomsdepressie.

In deel 1 van het proefschrift werd gefocust op de associatie tussen depressie symptoom profielen en het metabool syndroom als een belangrijke risicofactor voor vasculaire ziekte. Speciale aandacht werd daarbij gegeven aan de buikomtrek als maat voor abdominale obesitas. Abdominale obesitas is de centrale component van het metabool syndroom en juist dit vetweefsel blijkt metabool actief. In deel 2 van het proefschrift

werd gefocust op de associatie tussen depressie en de ernst van (subklinische) atherosclerose als directe marker voor vasculaire ziekte. In dit tweede deel werd tevens de interactie tussen subklinische vasculaire ziekte en neuroticisme, als tweede (meer traditionele) risicofactor voor depressie, onderzocht.

De studies in dit proefschrift werden vooral verricht bij personen van middelbare en oudere leeftijd binnen de Nijmegen Biomedical Study (NBS), een bevolkingsstudie in Nijmegen bij mensen tussen de 20 en 90 jaar. Daarnaast werd één studie verricht binnen de Longitudinal Aging Study Amsterdam (LASA), een prospectieve cohort studie bij mensen tussen 55 en 85 jaar en één studie binnen de Netherlands Study of Depression in Older Persons (NESDO), een multi-site naturalistiche cohort studie met als doel het beloop en gevolgen van depressie bij oudere mensen te onderzoeken.

Depressie symptoom profielen en het metabool syndroom

Het metabool syndroom, ook wel syndroom X genoemd, is een cluster van vasculaire risicofactoren. Het is volgens de definitie van de International Diabetes Federation (IDF) aanwezig wanneer er sprake is van abdominale obesitas (gedefinieerd als buikomtrek met ethniciteit specifieke waarden of als de Body Mass Index groter is dan 30 kg/m^2) en daarnaast twee van de volgende vier kenmerken aanwezig zijn: 1) Hypertriglyceridemie (triglyceriden groter of gelijk aan 150mg/dL of behandeling voor hypertriglyceridemie), 2) Verlaagd HDL cholesterol (kleiner dan 40 mg/dL bij mannen en 50 mg/dL bij vrouwen of voordien daarvoor behandeld), 3) Verhoogde bloeddruk (systolische bloeddruk hoger of gelijk aan 130 mmHg en diastolische bloeddruk hoger of gelijk aan 85 mmHg of behandeld voor een vooraf gediagnosticeerde hypertensie) en 4) Stijging van de nuchtere glucose (groter of gelijk aan 100 mg/dL) of een voorheen gediagnosticeerde Diabetes Mellitus type 2. De aanwezigheid van het metabool syndroom is een risicofactor voor het optreden van hart- en vaatziekten. Verschillende studies hebben ook een verband gevonden tussen depressie en het metabool syndroom. In hoofdstuk 2 en 3 hebben we deze bevindingen verdiept door specifiek de associatie tussen depressie symptoom profielen en het metabool syndroom en de verschillende maten van obesitas (Body Mass Index, buikomtrek, Taille-Heup-Ratio) te onderzoeken in de bevolking bij een groep mensen tussen 50 en 70 jaar die deelnamen aan de Nijmegen Biomedical Study (NBS).

In hoofdstuk 2 toonden we aan dat depressieve symptomen (somscore op de Beck Depression Inventory (BDI)) significant geassocieerd zijn met de aanwezigheid van het metabool syndroom. Er werd een nog sterker verband gevonden met het aantal componenten van het metabool syndroom. De associatie tussen het metabool syndroom en depressieve symptomen werd primair bepaald door het somatisch-affectieve symptoomcluster van depressie. Onderzoek naar sexe verschillen liet zien, dat bij mannen buikomtrek, triglyceriden en HDL-cholesterol de variantie in depressieve symptomen verklaarde, terwijl bij vrouwen dit beperkt was tot de buikomtrek. Hoewel de onderliggende pathofysiologische mechanismen van de associatie tussen metabole stoornissen en depressie verhelderd moeten worden, zou toekomstig onderzoek rekening moeten houden met zowel sexe-verschillen als het specifieke fenotype van depressie dat geassocieerd is met de metabole stoornissen.

Depressie symptoom profielen, ouderdomsdepressie en obesitas

In hoofdstuk 3 hebben we de associatie tussen depressie en obesitas verder onderzocht. Eerdere studies naar dit verband hielden geen rekening met zowel de verschillende depressie symptoom profielen als de verschillende manieren om obesitas te meten. We vonden, net zoals in een eerdere studie, dat er een U-vormige relatie is tussen Body Mass Index (BMI) en depressieve symptomen. Na het excluderen van de mensen met ondergewicht, werd een positieve correlatie gevonden tussen BMI en alle verschillende maten van depressieve symptomen (somscore BDI, cognitief- en somatisch affectieve symptoomcluster). Deze bevindingen suggereren dat depressieve symptomen bij personen met obesitas zowel door psychologische als somatische mechanismen kunnen worden verklaard. De maten voor viscerale obesitas (buikomtrek en taille-heup-ratio) waren echter specifiek geassocieerd met het somatisch-affectieve symptoomcluster. Dus adominale obesitas (buikomtrek), die meer indicatief is voor het vasculaire risico dan algemene obesitas (BMI), is meer geassocieerd met somatisch-affectieve depressieve symptomen dan met cognitief-affectieve depressieve symptomen. Mogelijk kunnen deze symptomen primair toegeschreven worden aan een (subklinische) somatische conditie.

Hoewel de verschillen tussen mannen en vrouwen niet significant waren, bleek de effect-grootte voor vrouwen groter dan voor mannen in alle maten voor depressieve symptomen in relatie tot BMI en buikomtrek. Sexe verschillen kunnen verklaard worden doordat vrouwen eerder dan mannen gestigmatiseerd worden als er sprake is van overgewicht.

In hoofdstuk 4 onderzochten we of het verband tussen buikomtrek en depressie in de bevolking ook in een klinisch depressieve groep ouderen (60 jaar of ouder) zou bestaan. We onderzochten het verband binnen de Netherlands Study of Depression in Older Persons (NESDO). Depressieve oudere patiënten hadden echter een significant lagere buikomtrek in vergelijking met de niet-depressieve controlegroep. Gegevens uit de bevolkingsstudie betreffende de positieve associatie tussen depressieve symptomen en obesitas kunnen dus niet gegeneraliseerd worden naar patiënten die aan een ouderdomsdepressie leiden. Binnen de groep depressieve ouderen bleek op basis van multipele lineaire regressie analyses wel dat zowel de ernst van depressie (gemeten met de Inventory of Depressive Symptoms) als aan de duur van depressie gerelateerde kenmerken (leeftijd van begin van depressie, duur van de ziekte, dysthymie) geassocieerd waren met de buikomtrek. Alleen het verband tussen buikomtrek en de ernst van de depressie bleef significant wanneer de analyses werden gecorrigeerd voor de Body Mass Index als algemene maat voor overgewicht. Wederom vonden we dat het verband niet voor alle depressie symptoomdimensies gold; in de NESDO populatie bleek alleen de motivatie subschaal significant geassocieerd te zijn met de buikomtrek.

Visceraal vetweefsel is vet in de buikholte rond een aantal belangrijke organen zoals lever, pancreas en darmen. Visceraal vet is metabool actief door de afgifte van ontstekingseiwitten, ook wel adipokines genoemd. Het wordt verondersteld dat deze adipokines een milde, doch chronische ontsteking veroorzaken, die bijdraagt aan het negatieve effect van obesitas op de gezondheid. Sommige adipokines, zoals leptine, resistine en adiponectine zijn in eerder onderzoek in verband gebracht met stemmingsregulatie. In hoofdstuk 2 vonden we dat adiponectine niet het verband tussen depressieve symptomen en het metabool syndroom of de individuele componenten van het metabool syndroom, zoals de buikomtrek, kon verklaren. In hoofdstuk 4 vonden we dat een recent ontdekt adipokine, Neutrophil Gelatinase-Associated Lipocalin (NGAL), geassocieerd was met de ouderdomsdepressie, maar alleen in de subgroep van patiënten met een pathologisch verhoogde buikomtrek. Deze bevinding zou dus de relatie tussen metabole activiteit van visceraal vet en depressieve symptomen kunnen verklaren, maar onze bevindingen over adiponectine toont aan dat er specifieke associaties zouden kunnen bestaan met de verschillende adipokines.

Depressie symptoom profielen, atherosclerose en neuroticisme

Het verband tussen depressieve symptomen en vasculaire ziekte is vooral aangetoond in studies die naar klinisch manifeste vasculaire ziekte keken zoals bij patiënten met een hartinfarct of cerebrovasculair accident (CVA). Aangezien een dergelijke manifeste vasculaire ziekte veelal het resultaat is van een jarenlange verergering van atherosclerose, onderzochten we in hoofdstuk 5 of depressie en depressie symptoom profielen ook geassocieerd zijn met atherosclerose. Deze studie werd eveneens uitgevoerd bij mensen tussen 50 en 70 jaar die deelnamen aan de Nijmegen Biomedical Study (NBS). Atherosclerose uit zich door een geleidelijke vervetting en verdikking van de wand van de slagaders in het lichaam. De mate van verdikking in de arteria carotis blijkt een goede weerspiegeling van de mate van atherosclerose. Deze verdikking, ook wel Intima Media Thickness (IMT) genoemd, blijkt een goede voorspeller voor het optreden van cardiovasculaire ziekten, zoals een hart- of herseninfarct. We vonden een significant verband tussen depressieve symptomen (somscore BDI) en subklinische atherosclerose gemeten middels de IMT, zowel in personen met als zonder een hartziekte. De relatie lijkt dus specifiek voor atherosclerotische ziekte onafhankelijk van vasculaire gebeurtenissen, zoals een CVA, in het verleden. De positieve associatie tussen depressieve symptomen en atherosclerose bleek primair bepaald te worden door het somatisch-affectieve symptoomcluster van depressie.

Het verband tussen depressieve symptomen en subklinische atherosclerose, viscerale obesitas en het metabool syndroom bij personen tussen de 50 en 70 jaar in de algemene bevolking zou dus verklaard kunnen worden door het somatisch-affectieve symptoomcluster van de depressieve symptomatologie. Mogelijk wijzen deze symptomen eerder op een (subklinische) somatische conditie dan op de aanwezigheid van een depressieve stoornis. Subklinische vasculaire ziekte en de risicofactoren obesitas en metabool syndroom kunnen dus mogelijk onterecht de score op depressie vragenlijsten verhogen en/of leiden tot een diagnose van een depressieve stoornis. Dit zou een verklaring kunnen zijn waarom behandeling van depressie bij bijvoorbeeld hartpatiënten nauwelijks effect sorteert op de vasculaire uitkomst.

Vervolgens vroegen we ons af of en hoe subklinische vasculaire ziekte zou interacteren met neuroticisme, een andere belangrijke risicofactor voor het ontstaan van de ouderdomsdepressie, in het verklaren van de variantie van deze depressieve symptoom profielen. Gebaseerd op eerdere studies, verwachtten we dat atherosclerose (gemeten met IMT)

en neuroticisme negatief zouden interacteren met betrekking tot de aanwezigheid van depressieve symptomen.
In hoofdstuk 6 hebben we beschreven dat in onze studie neuroticisme zowel geassocieerd was met het totaal aantal depressieve symptomen (somscore BDI) als met de cognitief-affectieve en somatisch-affectieve symptomen afzonderlijk. Deze associaties waren veel sterker dan de associatie tussen depressieve symptomen en atherosclerose. Des te meer opmerkelijk is het dat neuroticisme tot op heden zo onderbelicht is geweest in onderzoek naar de ouderdomsdepressie. We vonden een negatieve associatie tussen neuroticisme en atherosclerose in het verklaren van de variantie van de cognitief-affectieve symptomen van depressie maar niet van de somatisch-affectieve symptomen. Het effect van neuroticisme in het verklaren van depressieve symptomen vermindert dus naarmate er meer atherosclerose aanwezig is. Dit zou verklaard kunnen worden door de aanwezigheid van apathie ten gevolge van de cerebrovasculaire ziekte en dit past bij de hypothese van vasculaire apathie (hoofdstuk 6).

Laag neuroticisme als marker voor subklinische vasculaire ziekte in de ouderdomsdepressie

Gebaseerd op eerdere bevindingen, veronderstelden we in hoofdstuk 7 dat het verband tussen depressie en het optreden van vaatziekten gedeeltelijk wordt veroorzaakt doordat de onderliggende vasculaire ziekte op latere leeftijd leidt tot hogere depressiescores. Feitelijk keken we dus op een andere manier naar de heterogeniteit van het ontstaan van depressieve symptomen bij ouderen. We verwachtten dat de vasculaire depressie, met een volgens definitie hoge etiologische bijdrage van vasculaire ziekte, het risico op een cerebro vasculair accident (CVA) vergroot, terwijl de met neuroticisme geassocieerde depressie dat niet doet.
Eerder werd aangetoond dat depressie alleen bij hartpatiënten het optreden van een CVA voorspelde, maar niet bij personen zonder een cardiale aandoening. We maakten gebruik van dezelfde dataset uit de Longitudinal Aging Study Amsterdam (LASA), een bevolkingsonderzoek met een 9-jaars follow up bij mensen van 55 jaar en ouder. We toonden aan dat bij personen zonder cardiale aandoening depressie wel de incidentie van CVA voorspelt, maar alleen bij diegenen met een lage score op neuroticisme en niet bij degenen met een hoge score op neuroticisme. De balans tussen de twee belangrijke pathofysiologische mechanismen van de ouderdomsdepressie, (subklinische) vasculaire ziekte en neuroticisme, zou een belangrijke mogelijkheid kunnen bieden voor profilering. Daarmee zou het een indicatie kunnen geven om welk subtype van depressie het gaat met een eventuele uitkomst van behandeling. Eerste resultaten van kleine, doch gerando-

miseerde behandelstudies wijzen inderdaad op een betere uitkomst van behandeling als deze meer specifiek gefocust is op deze onderliggende mechanismen.

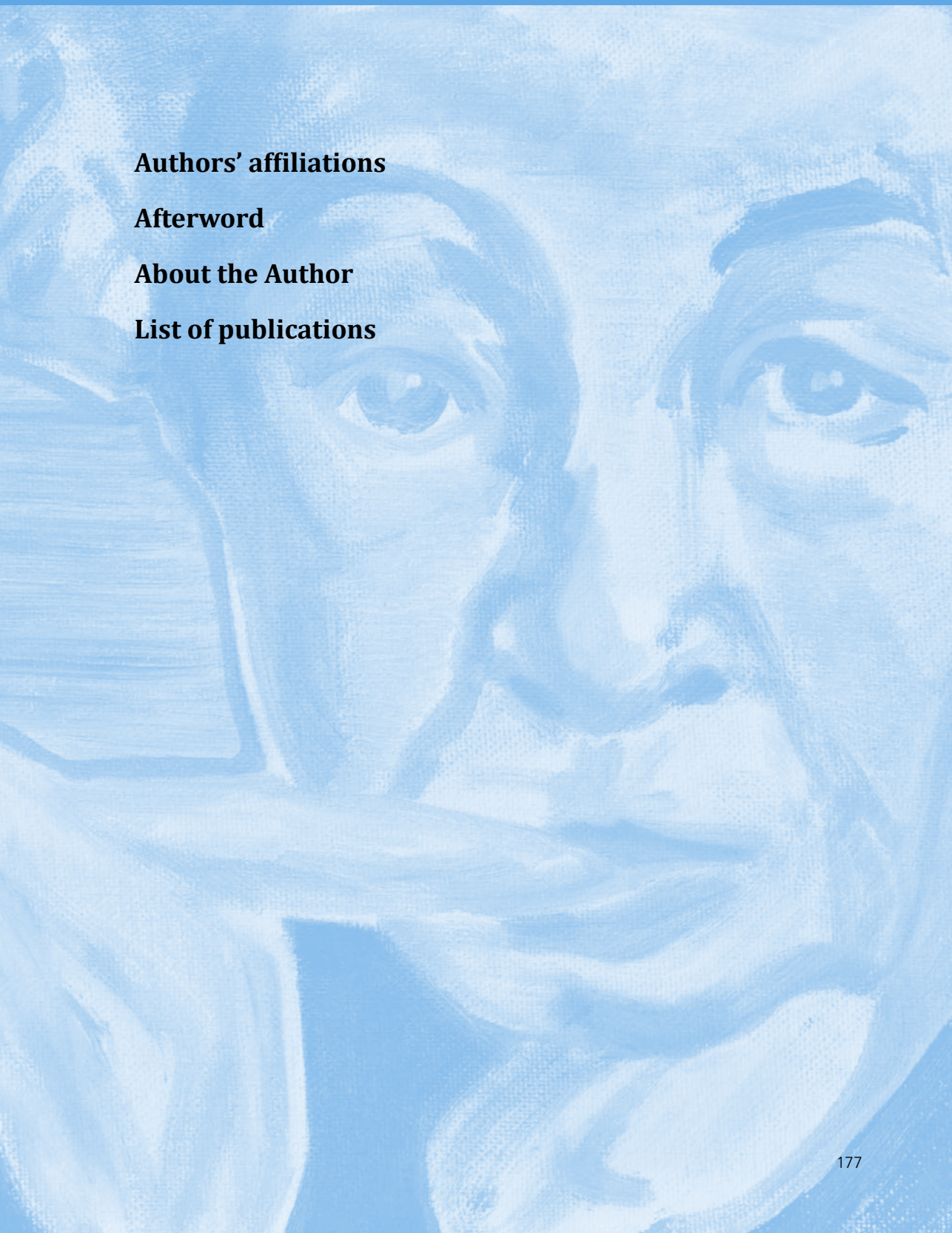
Conclusies

Dit proefschrift onderzocht de associatie tussen de ouderdomsdepressie en subklinische vasculaire ziekte, rekening houdend met verschillende depressie symptoom clusters en neuroticisme. Er kan geconcludeerd worden dat subklinische vasculaire ziekte geassocieerd is met depressieve symptomen op latere leeftijd. Meer specifiek zijn depressieve symptomen op latere leeftijd geassocieerd met het metabool syndroom, obesitas en gegeneraliseerde atherosclerose. Deze associaties kunnen gedeeltelijk verklaard worden door de verhoogde niveaus van adipokines, hoewel deze associaties niet consistent zijn gebleken voor de verschillende adipokines. De associaties tussen subklinische vaatziekten en depressieve symptomen bestaan met name met de somatisch-affectieve symptomen (gemeten met de Beck Depression Inventory). We hebben laten zien dat het relevant is subklinische vasculaire ziekte en neuroticisme als twee verschillende pathofysiologische mechanismen van de ouderdomsdepressie te bestuderen. Enerzijds verklaart neuroticisme minder van de variantie in depressieve symptomen in de aanwezigheid van subklinische vasculaire ziekte. Anderzijds is depressie in de afwezigheid van neuroticisme suggestief voor klinisch relevante subklinische vasculaire ziekte.

Er zouden dus argumenten kunnen zijn voor aanpassingen van de criteria van een depressieve stoornis bij patiënten met atherosclerose, viscerale obesitas en het metabool syndroom met minder nadruk op somatisch-affectieve symptomen. Vanuit klinisch oogpunt zou gesproken kunnen worden van een subtype van de ouderdomsdepressie met specifieke onderliggende etiologische mechanismen. Patiënten die leiden aan dit subtype van depressie kunnen profijt hebben van goede behandeling van de vasculaire ziekte en behandelprogramma's waarin ook lichamelijke oefeningen zoals wandelen of hardlopen zijn opgenomen. Deze versterken immers spieren en skelet, verminderen obesitas en beïnvloeden depressie bovendien positief. Omgekeerd is depressie geassocieerd met een lagere therapietrouw en zouden interventies voor medische problemen bij patiënten met atherosclerose, obesitas en metabool syndroom juist profijt kunnen hebben van een effectieve gelijktijdige behandeling van de depressie. Dit pleit voor een multidisciplinaire aanpak van de ouderdomsdepressie door psychiaters en klinisch geriaters, zo nodig aangevuld met (vasculair) internisten en/of cardiologen.

Dit proefschrift illustreert de complexiteit en heterogene aard van de ouderdoms-

depressie. Meer aandacht voor de specifieke symptoom profielen van depressie en de (interactie tussen de) twee belangrijke pathofysiologische mechanismen van de ouderdomsdepressie zouden klinische beslissingen kunnen beïnvloeden. Uiteraard moeten bevindingen en conclusies uiteindelijk bevestigd worden in prospectieve cohort studies en klinische trials met depressieve ouderen. Dergelijke studies zouden voldoende groot moeten zijn om subgroepen te kunnen identificeren met een slechtere prognose met betrekking tot de fysieke gezondheid. Toekomstige cohort studies zouden de meest relevante concepten in detail moeten bestuderen. Allereerst zou zowel de hele reeks van adipokines onderzocht moeten worden als de relatieve impact van de buikomtrek, gemeten met zowel de anthropometrische indices als een MRI, op de ouderdomsdepressie. Ten tweede moet bij het meten van de ouderdomsdepressie rekening gehouden worden met de verschillende symptoomdimensies van depressie en andere psychologische concepten als angst, somatisatie en persoonlijkheid. Deze concepten zouden bij voorkeur gemeten moeten worden zowel door zelfrapportage als een semi-gestructeerd interview dat wordt afgenomen door een getrainde professional. Vanuit efficiency oogpunt is het aan te bevelen bevolkingsstudies uit te breiden met cohort studies van depressieve patiënten. Ten slotte zouden de fenotypische expressie van depressie, vasculaire risicofactoren en perifere maten voor subklinische vasculaire gezondheid gerelateerd moeten worden aan de circuits in de hersenen die betrokken zijn bij stemmingsregulatie, door neuro-imaging en meer specifieke neuropsychologische testen toe te passen.



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AFTERWORD

The process of this thesis was informative and inspiring. I have learned a lot. The persons who have supported me in different ways know how grateful I am for their contributions. In the future I hope to spend more free time together with them or to intensify working together and to meet in new exciting research.

ABOUT THE AUTHOR

Radboud Marijnissen was born in Breda, the Netherlands, on December 1st 1965. After graduation in 1983 from secondary school (VWO) at the 'Onze Lieve Vrouwe Lyceum' in Breda, he started to study psychology at the Radboud University Nijmegen (RUN) in Nijmegen. The year after, in 1984, he switched to medicine at the Medical Faculty of the same university. As part of his internships, he worked e.g. at the Lagos University Teaching Hospital (LUTH) (Nigeria) and at Quthing Hospital (Lesotho). In his research-internship he examined the cognitive functioning of older people in care homes (Supervision: Prof. Dr. F.G. Zitman, Department of Psychiatry, RUN, Nijmegen). He obtained his medical degree in 1992 and worked afterwords as a house officer not in training at several psychiatric departments. In 1995 he started his residency in psychiatry at de Gelderse Roos / Pro Persona in Wolfheze (Supervisors: Dr. C.V. de Blécourt and later Dr. A. Kaasenbrood) and was registered as a psychiatrist in 1999.

From 1999 till 2001 he worked as an old-age psychiatrist at the outpatient department for elderly of Altrecht in Utrecht. From 2001 till present he works as an old-age psychiatrist at de Gelderse Roos / Pro Persona in Arnhem (acute ward) and Wolfheze (long-term care). He is a consulting psychiatrist for a rehabiliation clinic in Arnhem and several nursing homes in the area of Arnhem and Apeldoorn. He worked as an acting first medical at de Gelderse Roos / Pro Persona in Arnhem (2003-2011).

Besides his clinical work for older psychiatric patients, his passion is to train medical doctors to become (preferably old-age) psychiatrists. From 2008 till 2013 he was acting director of the residency training program and from 2011 till present he is director of the old-age residency training program of Pro Persona. He worked as the secretary and member of the board of the department of old-age psychiatry of the Nederlandse Vereniging voor Psychiatrie (2003-2013). In 2014 he became medical director of the old age program of Pro Persona.

After some smaller scientific trips (especially writing case-reports with residents), in 2009 he became further involved in research and started this thesis under supervision of Prof. dr. R.C. Oude Voshaar and Prof. dr. R.A. Schoevers. Besides the scientific work of this thesis he is involved in research about the role of vitamine D deficiency in the late-life depression, longterm followup of patients with catatonic disorders and the assessment of personality traits and disorders in older people during an acute depressive episode.

Radboud lives together with August Peters (painter and graduated master in fashion design) since 1995.

Marijnissen RM, Wouts L, Schoevers RA, Bremmer MA, Beekman ATF, Comijs HC, Oude Voshaar RC. (2014) Depression in context of low neuroticism is risk factor for stroke: a 9-year cohort study. *Neurology; In press.*

Oude Voshaar RC, Derks WJ, Comijs HC, Schoevers RA, de Borst MH, Marijnissen RM. (2014) Antidepressants differentially related to 1.25-(OH)2 vitamin D3 and 25-(OH)2 vitamin D3 in late-life depression. *Transl Psychiatry;* 15;4e383. Doi: 10.1038/tp.2014.14.

van den Berg K, Marijnissen RM, van Waarde JA. (2014) Delirious mania: a severe syndrome with many faces. *Submitted.*

Marijnissen RM, Bus BAA, Schoevers RA, Wouts L, Holewijn S, Franke B, de Graaf J, den Heijer M, Buitelaar JK, Oude Voshaar RC. (2014) Atherosclerosis decreases the impact of neuroticism in late-life depression: Hypothesis of vascular apathy. *Am J Geriatr Psychiatry;* 22(8):801-10.

Marijnissen RM, Naude PJW, Comijs HC, Schoevers RA, Oude Voshaar RC. (2014) Waist circumference and Neutrophil Gelatinase-Associated Lipocalin in late-life depression. *Brain Behav Immun;* 37:231-9. doi: 10.1016/j.bbi.2013.12.021.

Marijnissen RM, Smits JEMP, Schoevers RA, van den Brink R, Holewijn S, Franke B, de Graaf J, Oude Voshaar RC (2013) Association between metabolic syndrome and depressive symptom profiles - sex-specific? *J Affect Disord;* 151(3):1138-42.

van Woelderen M, Marijnissen RM, Stalpers-Konijnenburg, Oude Voshaar RC. (2013) Resident old-age psychiatrists need training in the interpretation of cerebral imaging: a pituitary incidentaloma. *Tijdschr Psychiatr;* 55(8):625-30. Dutch.

Marijnissen RM, Derks WJ, Gaasbeek AB, Stalpers-Konijnenburg SC, Oude Voshaar RC. (2013) Alarming vitamin D deficiency in older psychiatric inpatients. *Journal of Aging, Research and Clinical Practice;* 2(01): 137-141.

Marijnissen RM, Bus BAA, Holewijn S, Franke B, Purandare N, de Graaf J, den Heijer M, Buitelaar JK, Oude Voshaar RC. (2012) Depressive symptoms and obesity in later life. *www.ageing.oxfordjournals.org.uk* Volume 41, Supplement 1, i76.

Halink DA, Marijnissen RM, Schut AA, Oude Voshaar RC. (2011) Drug Reaction Eosinophilia

and Systemic Symptoms induced by carbamazepine: DRESSed to kill. *Gen Hosp Psychiatry;* 33:412.e5-412.e8.

Stalpers-Konijnenburg SC, Marijnissen RM, Gaasbeek AB, Oude Voshaar RC. (2011) Can I have some sunshine to cheer me up? Vitamin D deficiency and depression in the elderly. *Tijdschr Psychiatr;* 53(6): 365-370. Dutch.

Marijnissen RM, Bus BAA, Holewijn S, Franke B, Purandare N, de Graaf J, den Heijer M, Buitelaar JK, Oude Voshaar RC. (2011) Depressive symptoms clusters are differentially associated with general and visceral obesity in later life. *J Am Geriatr Soc;* 59 (1): 67-72.

Bus BAA, Marijnissen RM, Holewijn S, Franke B, Purandare N, de Graaf J, den Heijer M, Buitelaar JK, Oude Voshaar RC. (2011) Depressive symptom clusters are differentially associated with atherosclerotic disease. *Psychol Med;* (10): 1-10.

Marijnissen RM, Bakker M, Stek ML. (2010) First manic episode in the elderly: consider a subdural haematoma due to head trauma as cause. *Ned Tijdschr Geneeskd;* 154(16): 755-759. Dutch.

Janse A, Marijnissen RM. (2009) Quetiapine-induced bradycardia without QT interval prolongation in an elderly woman. *Prim Care Companion J Clin Psychiatry;* 11(4):172-3.

Haverkort S, Jellesma-Eggenkamp MJ, Marijnissen RM. (2007) Psychiatric presentation of hypopituitarism in an elderly patient. *Tijdschr Psychiatr;* 49(2):119-23. Dutch.

van Lith EC, Marijnissen RM. (2006) Danger of social breakdown: compulsory admission, but not treatment? A case stuyd. *Tijdschr Psychiatr*; 48(8):655-9. Dutch.

Kok RM, Matthijsen AH, Marijnissen RM. (2005) Psychic consequences on the elderly of sexual abuse in their youth. *Ned Tijdschr Geneeskd;* 149(17):905-8. Dutch.

STELLINGEN BEHORENDE BIJ HET PROEFSCHRIFT

The weight of
subclinical vascular disease & neuroticism in
late-life depression

1. Bij een lage mate van neuroticisme is de ouderdomsdepressie een indicator voor subklinisch, doch klinisch relevant, vaatlijden. (Dit proefschrift)

2. In de algemene bevolking dienen de criteria voor een depressieve stoornis bij ouderen te worden aangepast met minder nadruk op somatisch-affectieve symptomen. (Dit proefschrift)

3. De invloed van de verschillende pathofysiologische mechanismen (subklinische vasculaire ziekte en neuroticisme) op depressie verandert met het ouder worden. (Dit proefschrift)

4. De positieve associatie tussen obesitas en depressieve symptomen, zoals die wordt gevonden bij ouderen in de bevolking is niet één op één vertaalbaar naar klinische populaties; vermoedelijk omdat enkel de meest kwetsbare ouderen in zorg komen. (Dit proefschrift)

5. Er moet zowel in onderzoek als in de klinische praktijk bij patiënten van middelbare en oudere leeftijd aandacht zijn voor de verschillende symptoom dimensies van depressie. (Dit proefschrift)

6. De hypothese dat adipokines de relatie tussen obesitas en depressie mediëren is verleidelijk, maar niet evidence based. (Dit proefschrift)

7. Aangezien de ouderenpsychiater bij patiënten met een ouderdomsdepressie naast psychologische ook somatische pathofysiologische mechanismen dient te evalueren, is in de opleiding tot ouderenpsychiater een somatische stage essentieel. (Dit proefschrift)

8. Het publiceren van case-reports door AIOS leidt tot meer wetenschappelijke output.

9. Hoewel de Evidence Based Mental Health ook de kwaliteit van de ouderenpsychiatrie geleidelijk doet toenemen, zal juist in dit vak de stelling “It is costly that is bought by experience” (R. Asham–1515-1568) altijd blijven gelden.

10. Bij ouderenpsychiaters, die pas op latere leeftijd daadwerkelijk starten met wetenschappelijk onderzoek, gaat ‘hel’ hand in hand met ‘YEAH!’.